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Hepatitis C virus (HCV) genome organization.

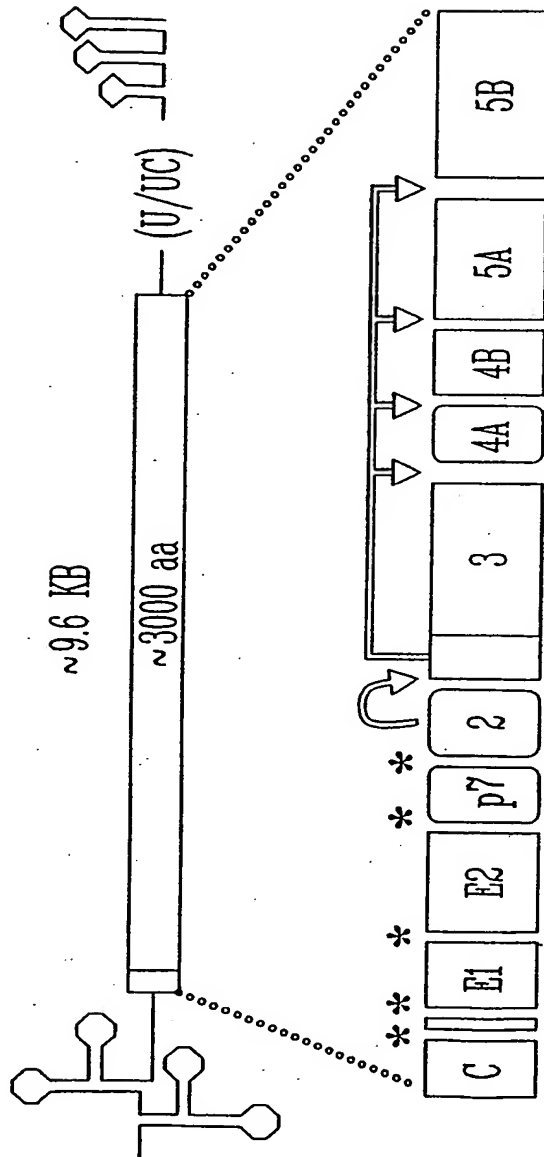


FIG. 1

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Hypothetical model of the HCV replication cycle

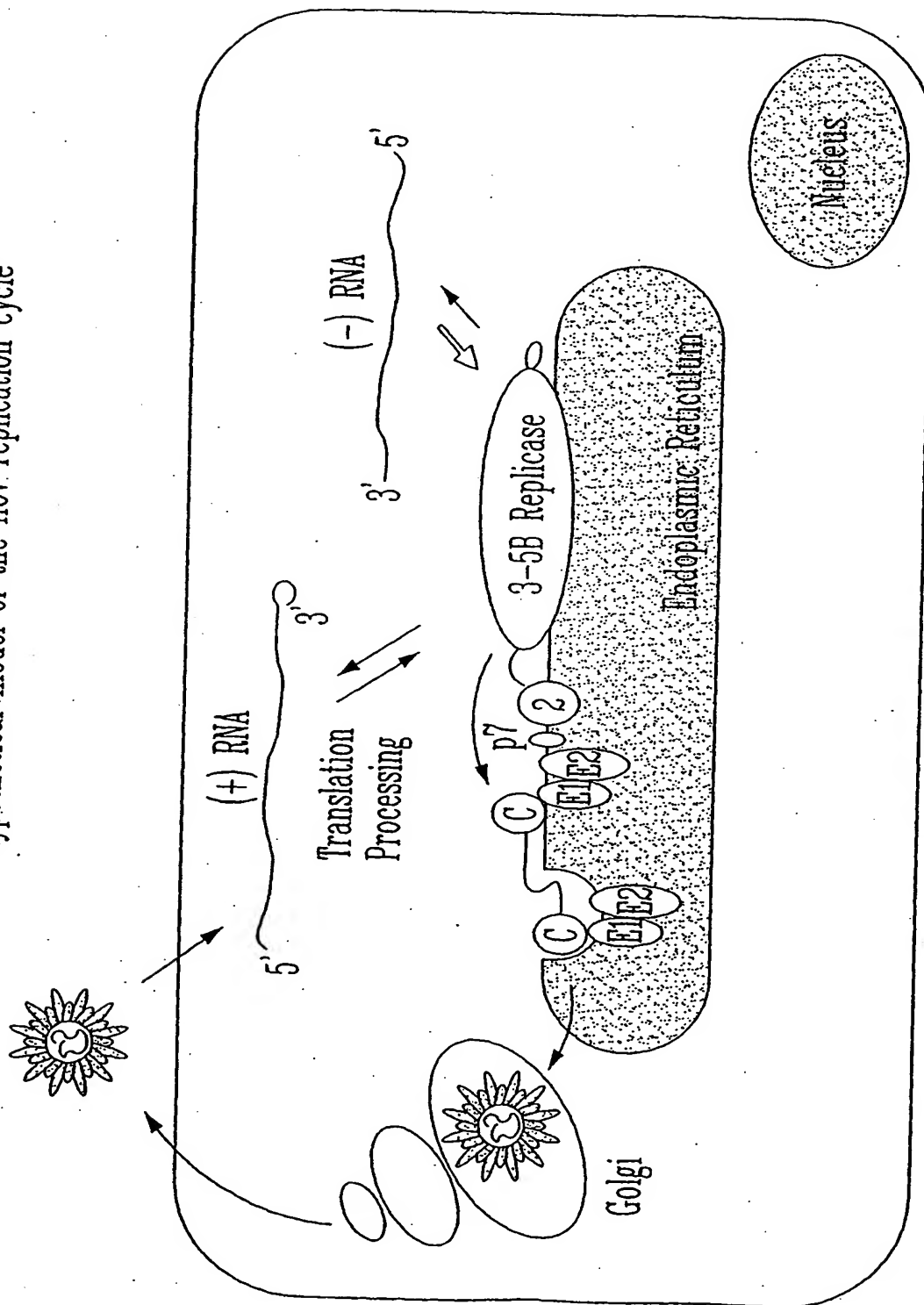


FIG. 2

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# Experimental Protocol.

HCV(+); HIV(-) donor.

HCV (-); HBV (-); HIV (-) donor.

Blood

Ficol  
extraction

PBMCs

Treated:  
T1, T2, T3

NT

Crosslinking to HCV IRES

Western blot

Putative Virus purification

RNA extraction

Infection of Huh-7 and others

✓

✓

✓

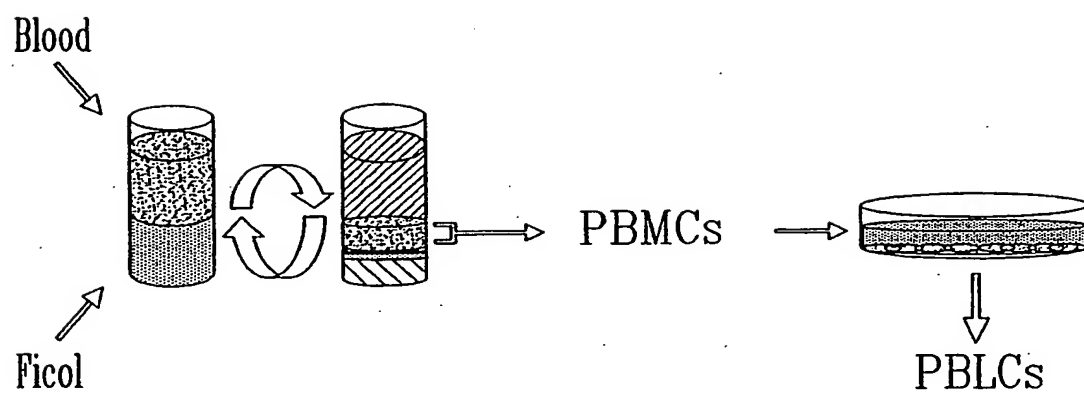
✓

✓

Fig. 3

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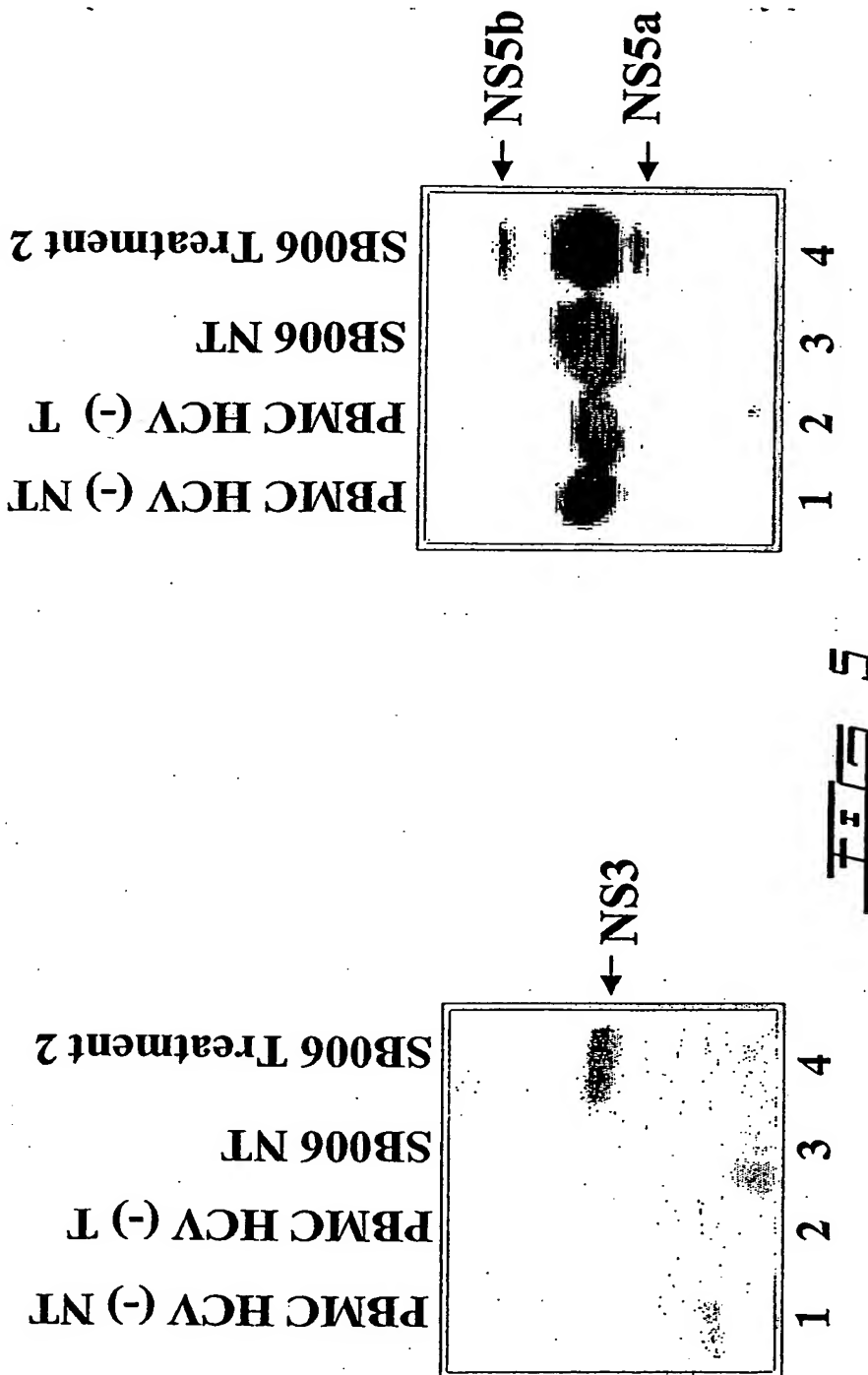
PBMC and PBLc purification from blood samples.

FIG. 4

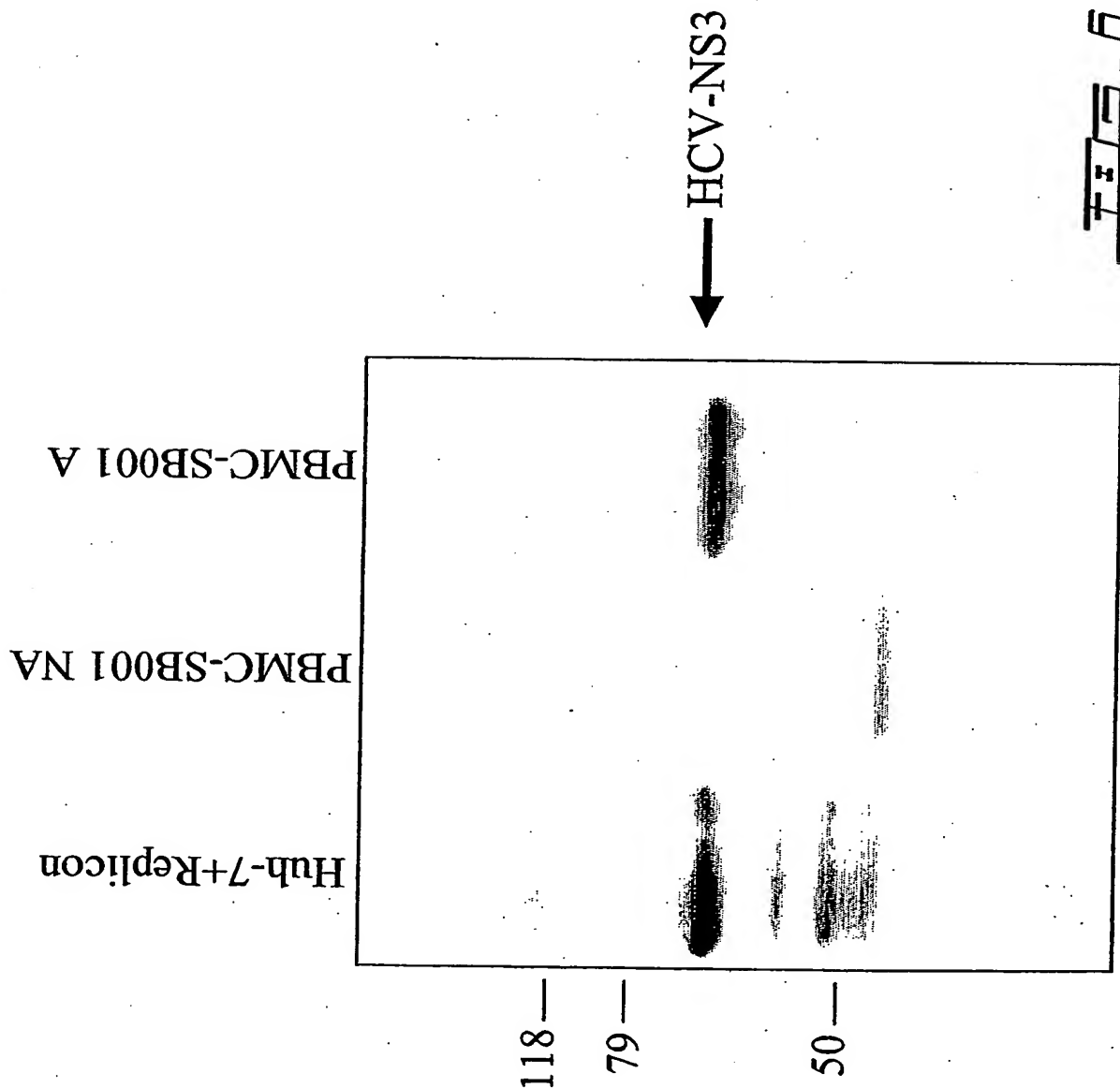
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**Detection of HCV NS3 and NS5 proteins in cell extracts from Treated  
PBMC from an HCV (+) patient.  
[Boeringeranti-NS3 polyclonal antibody]**



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# Time course of HCV-NS3 detection: PBMCs From patient MLL-001

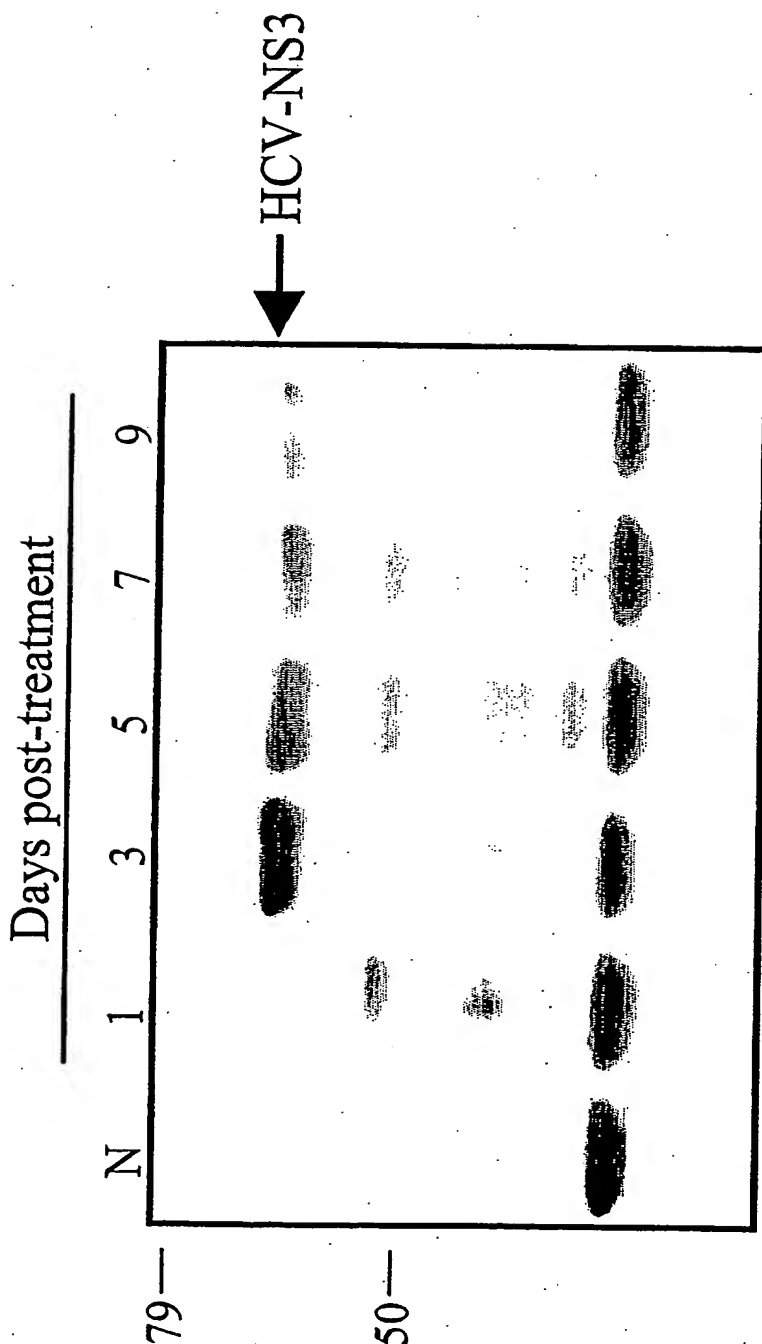
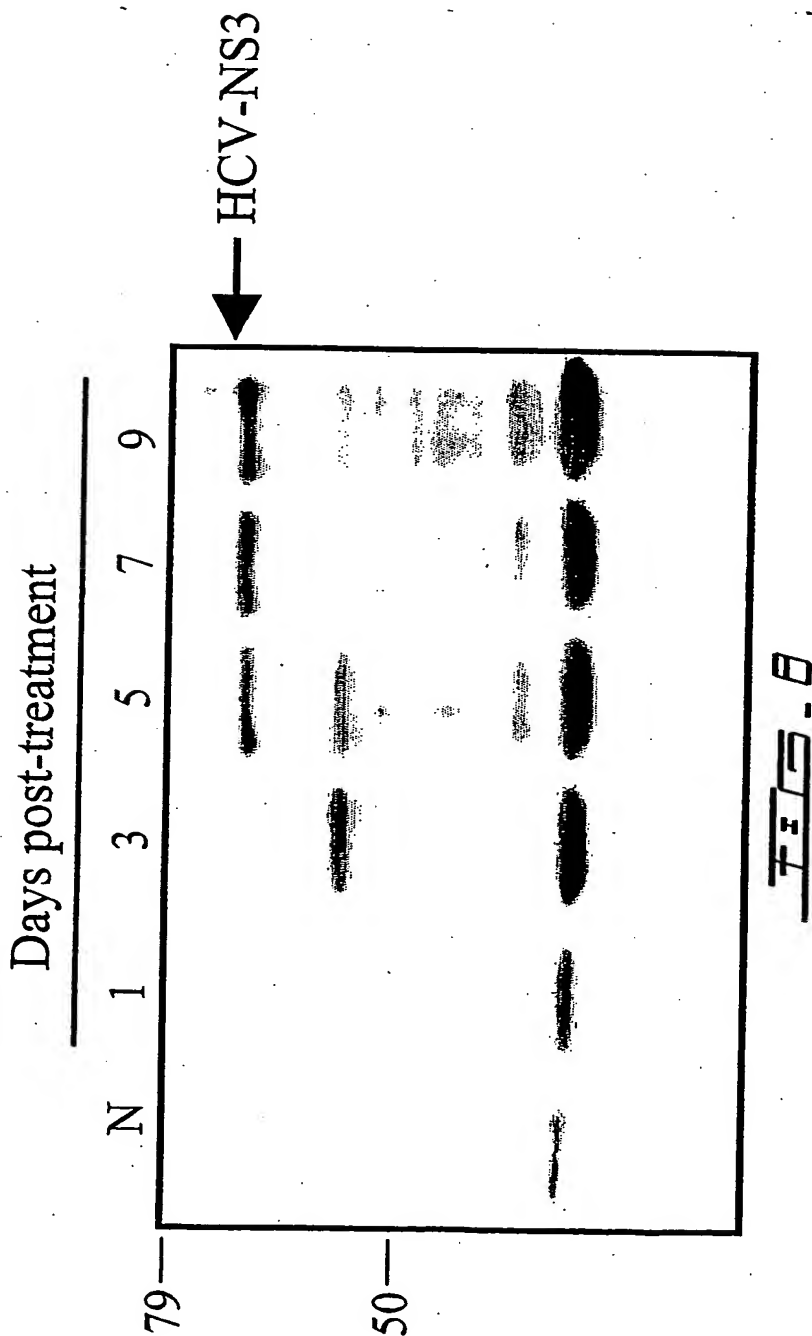


Fig. 7

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**Time course HCV-NS3 detection:  
PBMCs from patient MILL-002**





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# Detection of HCV-NS3 protein in treated (N3) PBMCs from HCV9+) donors

PBMCs  
HCV (-) donor.

Huh-7  
Huh-7+ replicon

PBMCs  
SB006

PBMCs  
SB004

PBMCs  
SB005

N A N A1 A2 N A1 A2

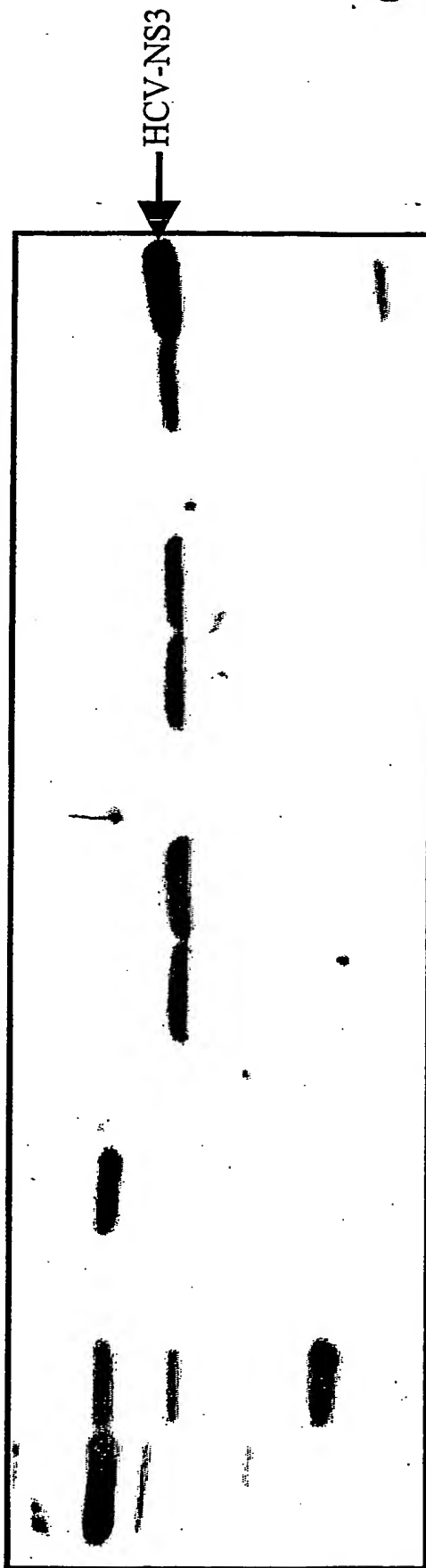
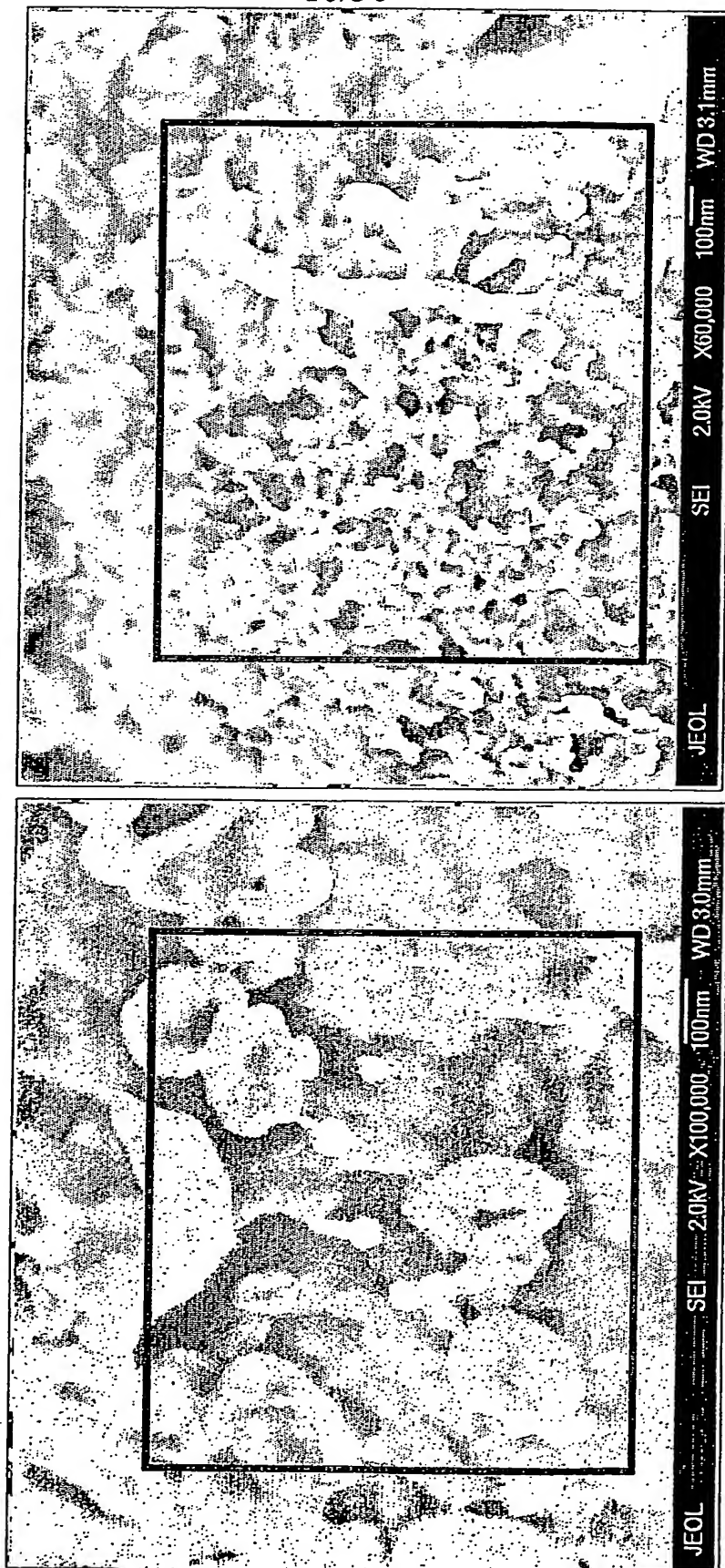


FIG. 9

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Detection of virus like particles by scanning electron microscopy



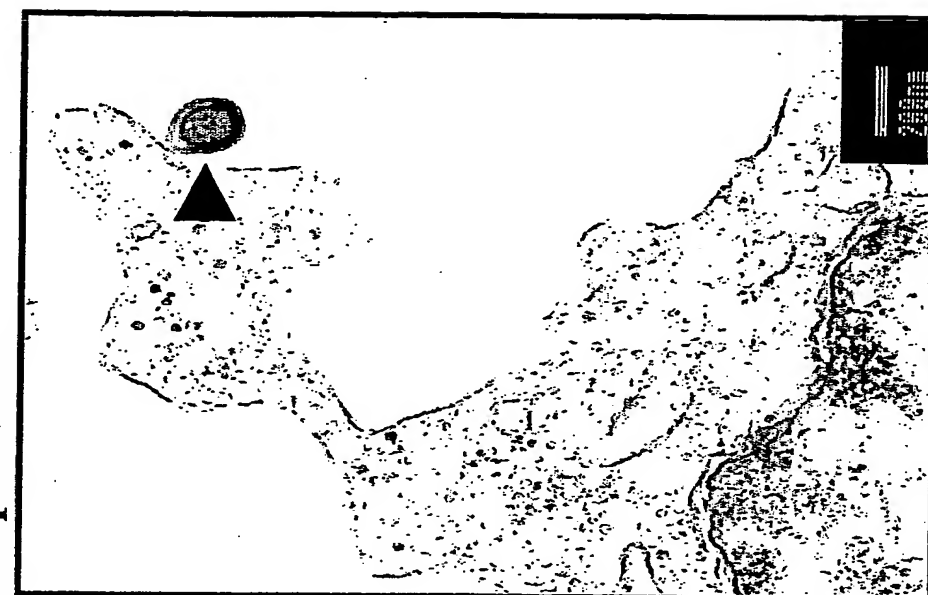
(-) Control

FIG. 10

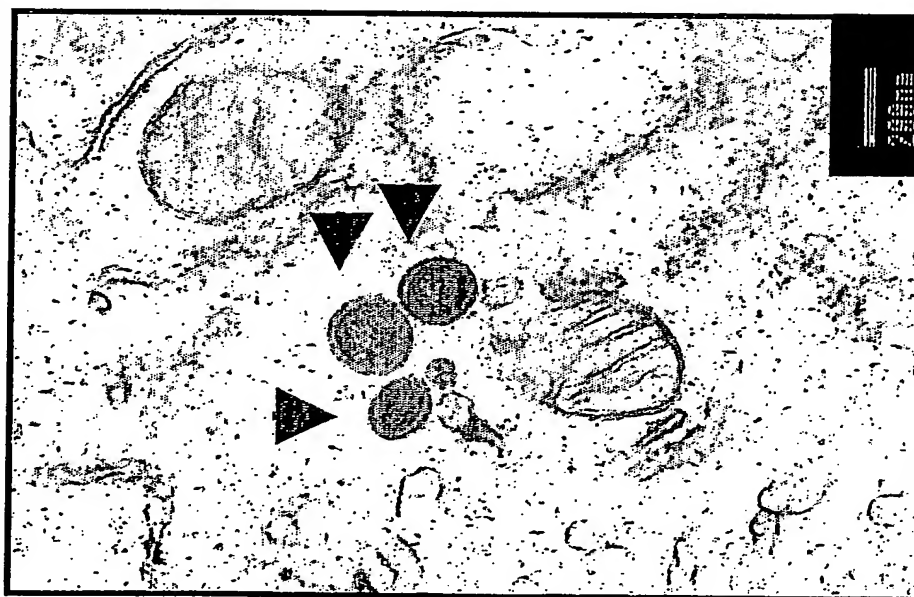
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**Electron microscopy of Activated PBLs;  
Detection of virus like particles**



200 nm



200 nm

FIG. 11

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Virus partial purification.

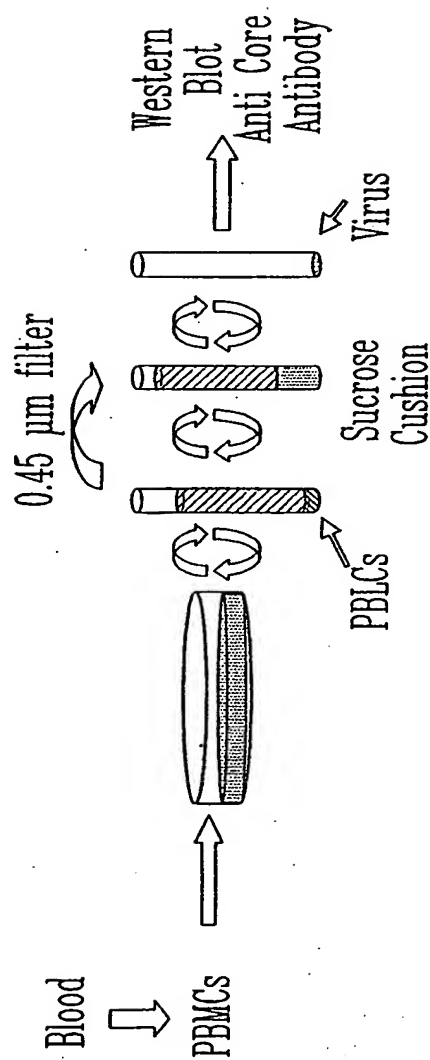
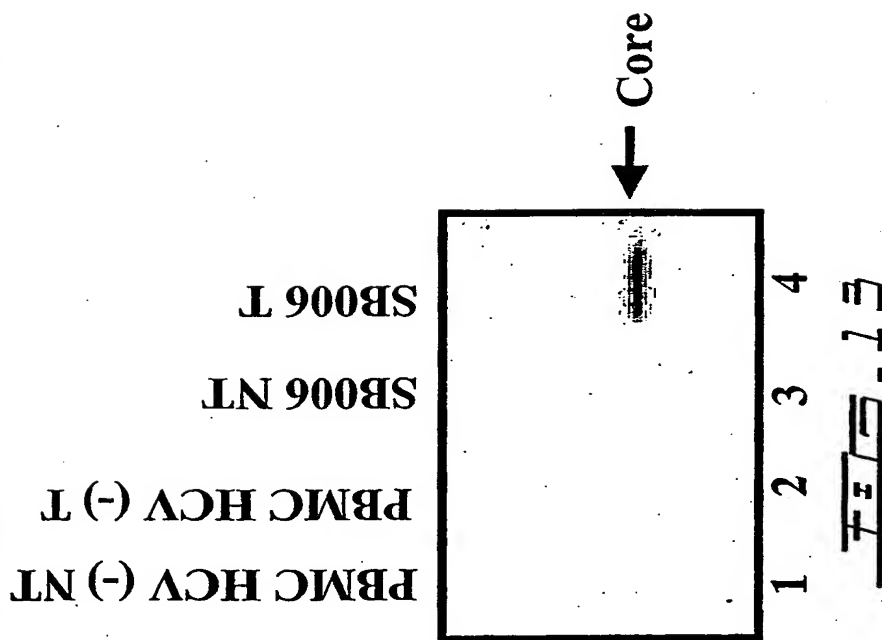


FIG. 12

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**Detection of HCV Core protein in supernatant of treated  
PBMC from an HCV (+) patient.  
[Maine biotechnology anti-Core monoclonal antibody]**



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**RNA Quantification I (virus copies/ng total RNA)**

Patient	HCV RNA In PBMC	Detection of Core (wb) in supernatant
---------	--------------------	---

After 4 days

SB004 NT	2x10 <sup>3</sup>	No
----------	-------------------	----

SB004 T	2x10 <sup>3</sup>	Yes
---------	-------------------	-----

SB006 NT	1.8 x10 <sup>3</sup>	No
----------	----------------------	----

SB006 T	2x10 <sup>2</sup>	Yes
---------	-------------------	-----

After 20 days

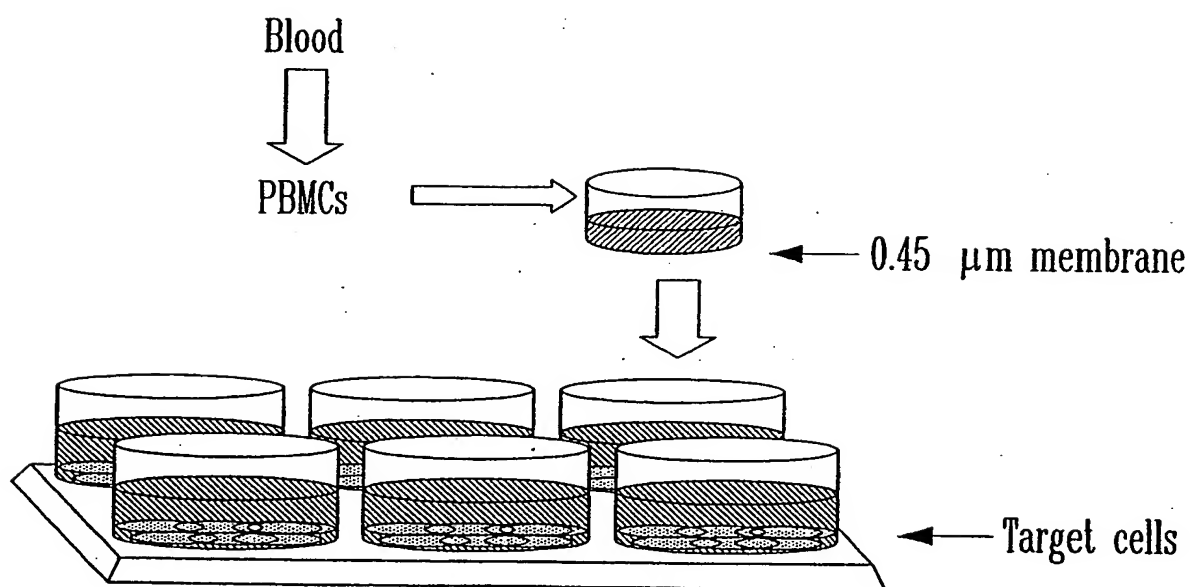
SB004	0.00
-------	------

SB006	0.00
-------	------

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## Infection assay; co-culture

FIG. 15

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**Infection of MT-4 cells**  
**RNA Quantification II (virus copies/ng total RNA)**

Patient	HCV RNA In PBMC	Detection of Core (wb) in supernatant	HCV RNA In MT-4
<u>After 10 days</u>			
SB001 NT	13	No	0.00
SB001 T	12	Yes	1600
<u>After 20 days</u>			
SB001	0.00		0.00
SB001	0.00		0.00

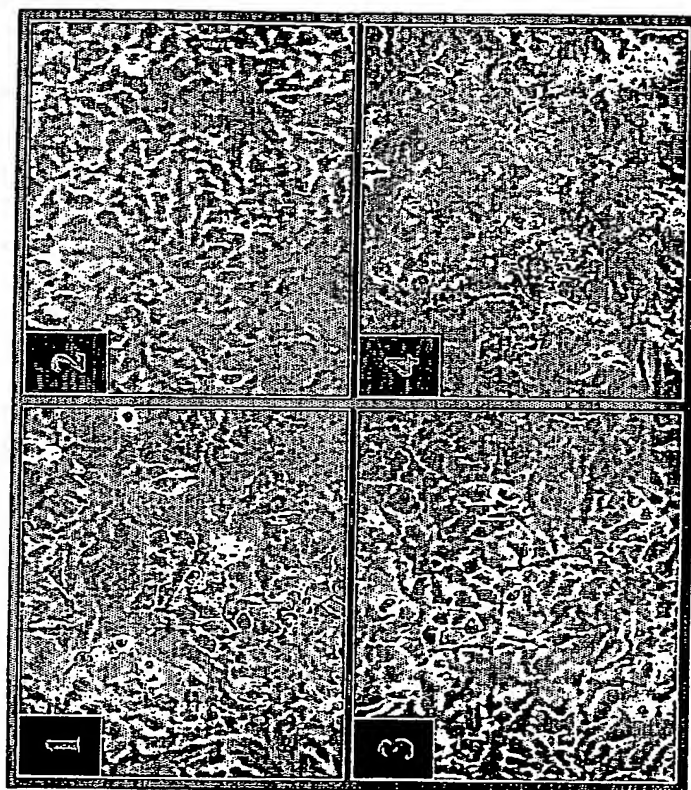
FEES - 16



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# Co-culture of Huh-7 and HCV (-) PBMCs.

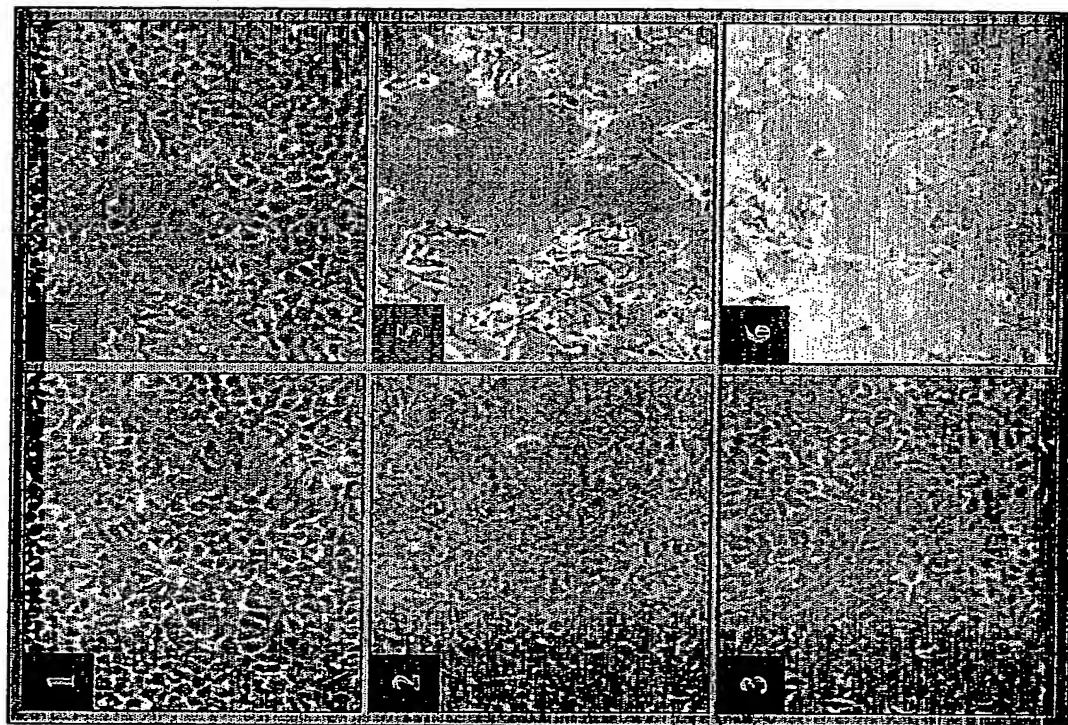


- 1- Huh-7
- 2- Huh-7 + PBMCs HCV (-) NT
- 3- Huh-7 + Treatment
- 4- Huh-7 + PBMCs HCV (-) T

FIG. 17

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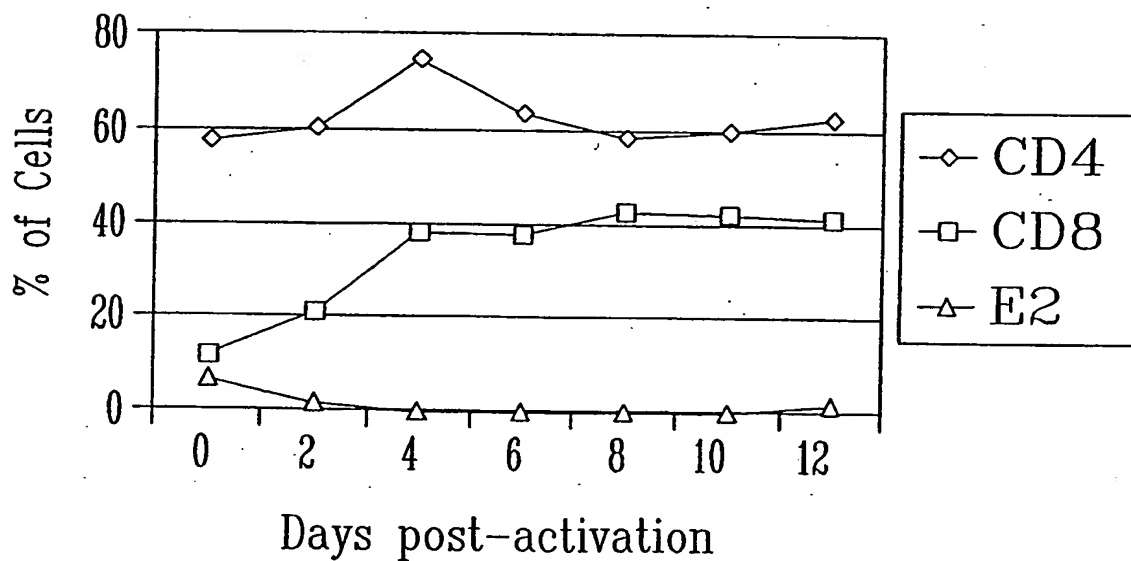
**Co-culture of Huh-7 and HCV (+) PBMS<sup>®</sup> Cs (SB006).**

1. Huh-7
- 2-3. Huh-7 + PBMCs HCV (+) NT
4. Huh-7 + Treatment
- 5-6. Huh-7 + PBMCs HCV (+) T

FIG. 18

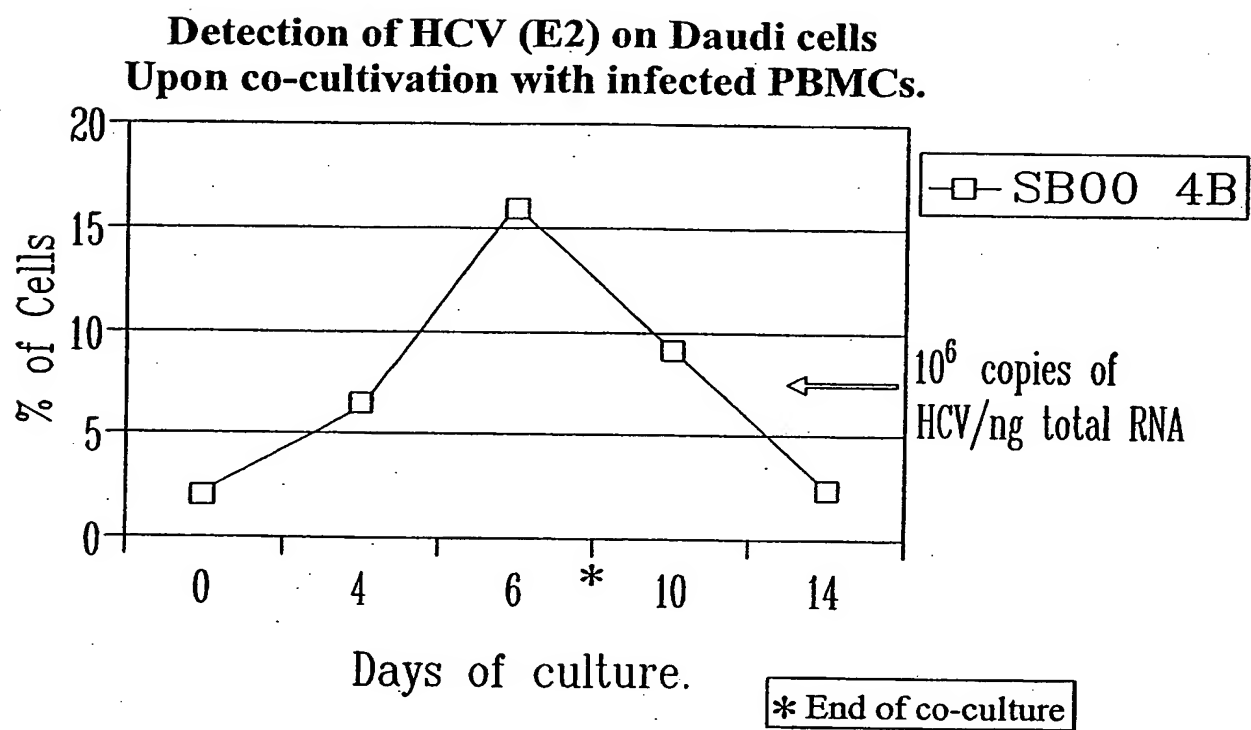
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PHA Activation of PBMCs from patient SB004;  
HCV is not in T cells

FIG. 19

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FIG. 20

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**Comparison of different activation treatments; PBMCs from donor MLL-010**

T+B cells											
T cells (T1)				B cells (T2)				(T3)			
Treatment				Treatment				Treatment			
N	2	4	8	12	2	4	8	12	2	4	Days

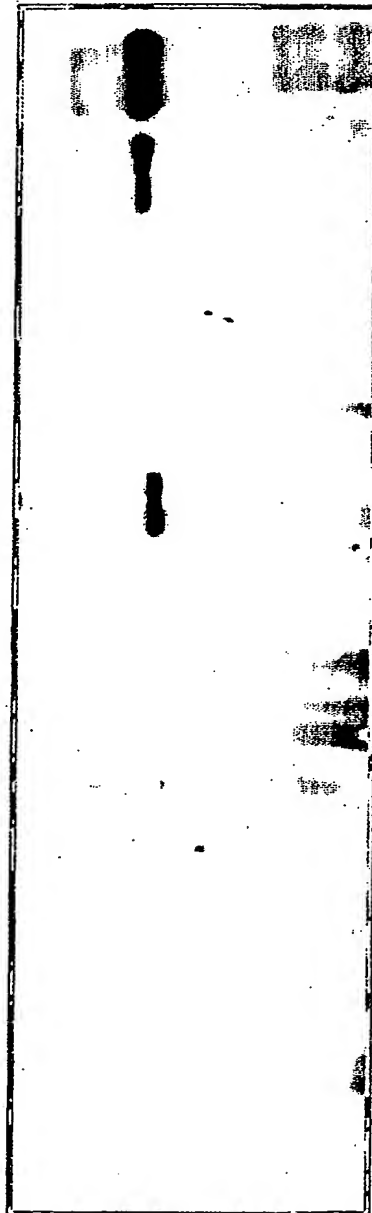


FIG. 21

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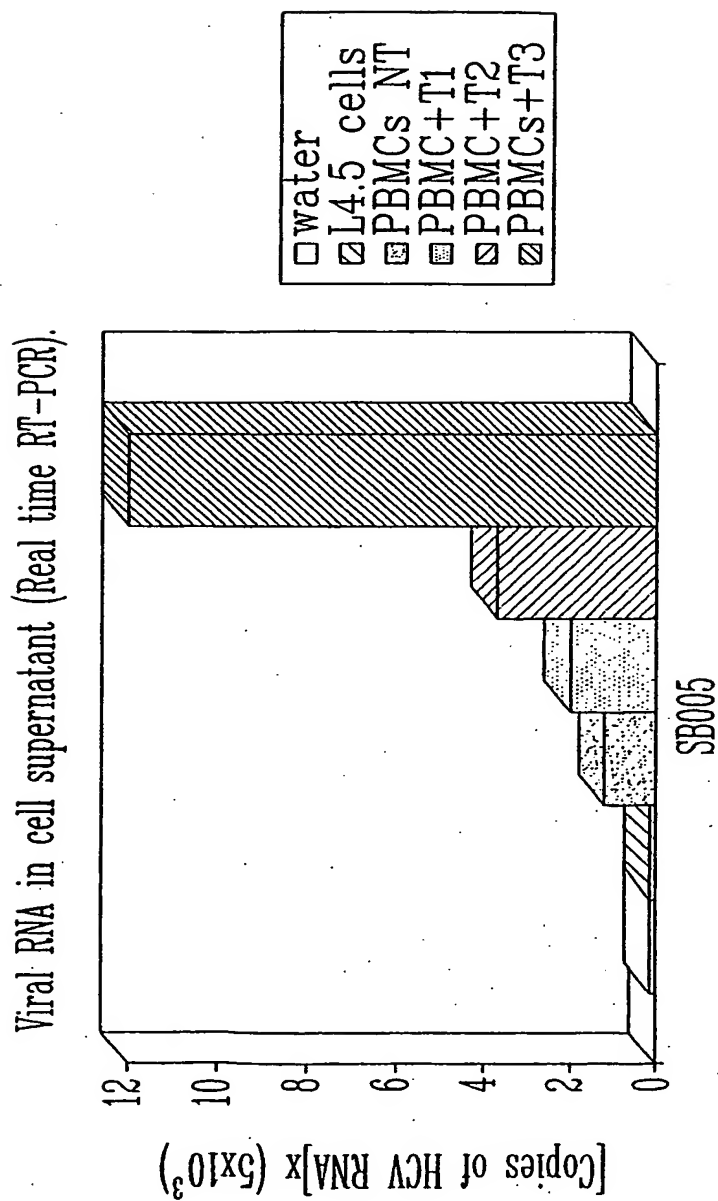


Fig. 22

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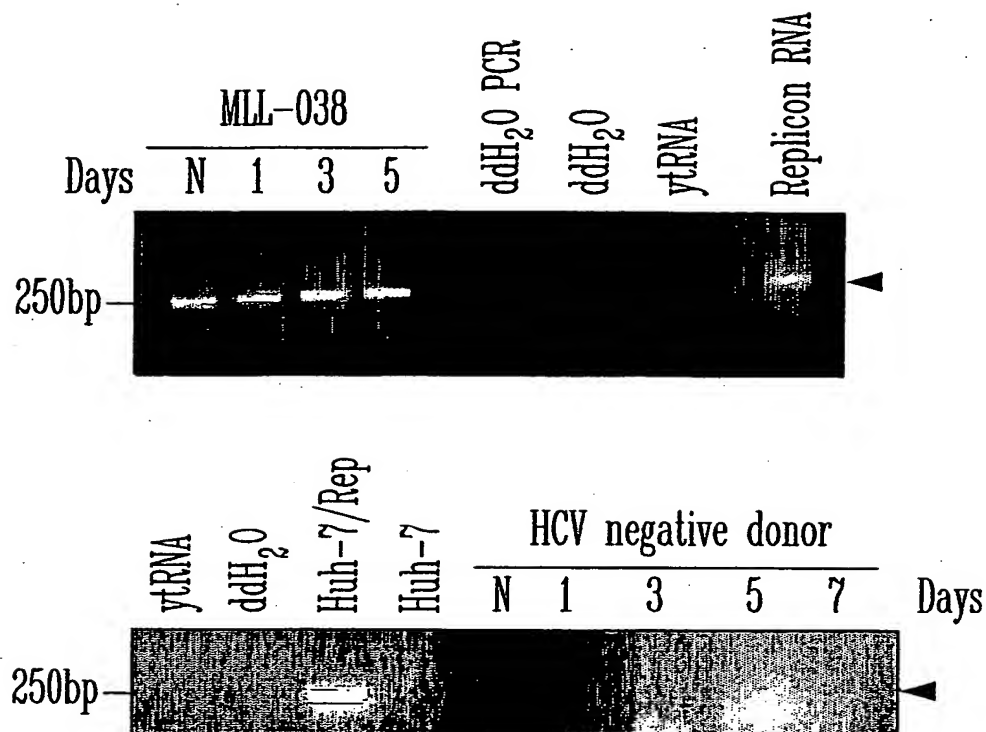


FIG. 23 A

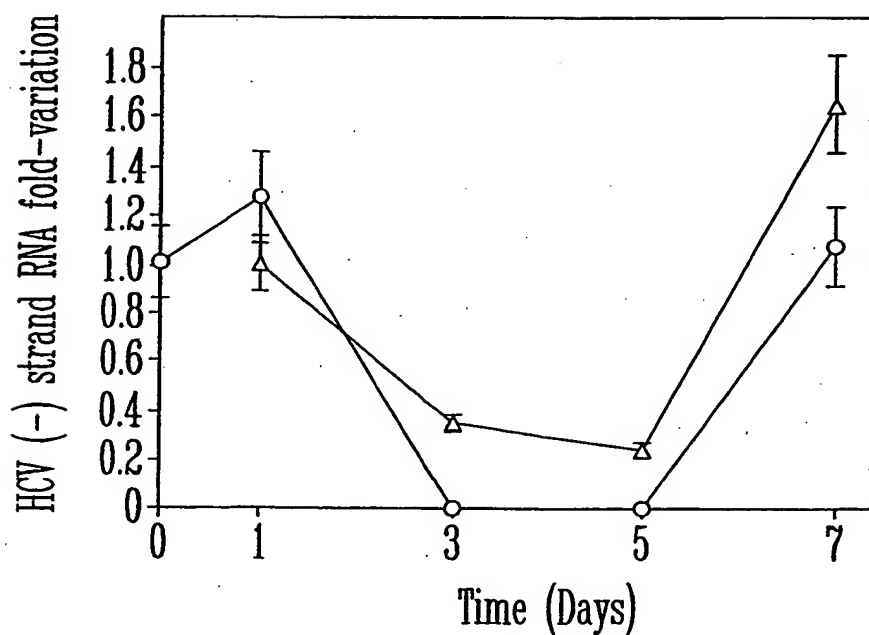


FIG. 23 B

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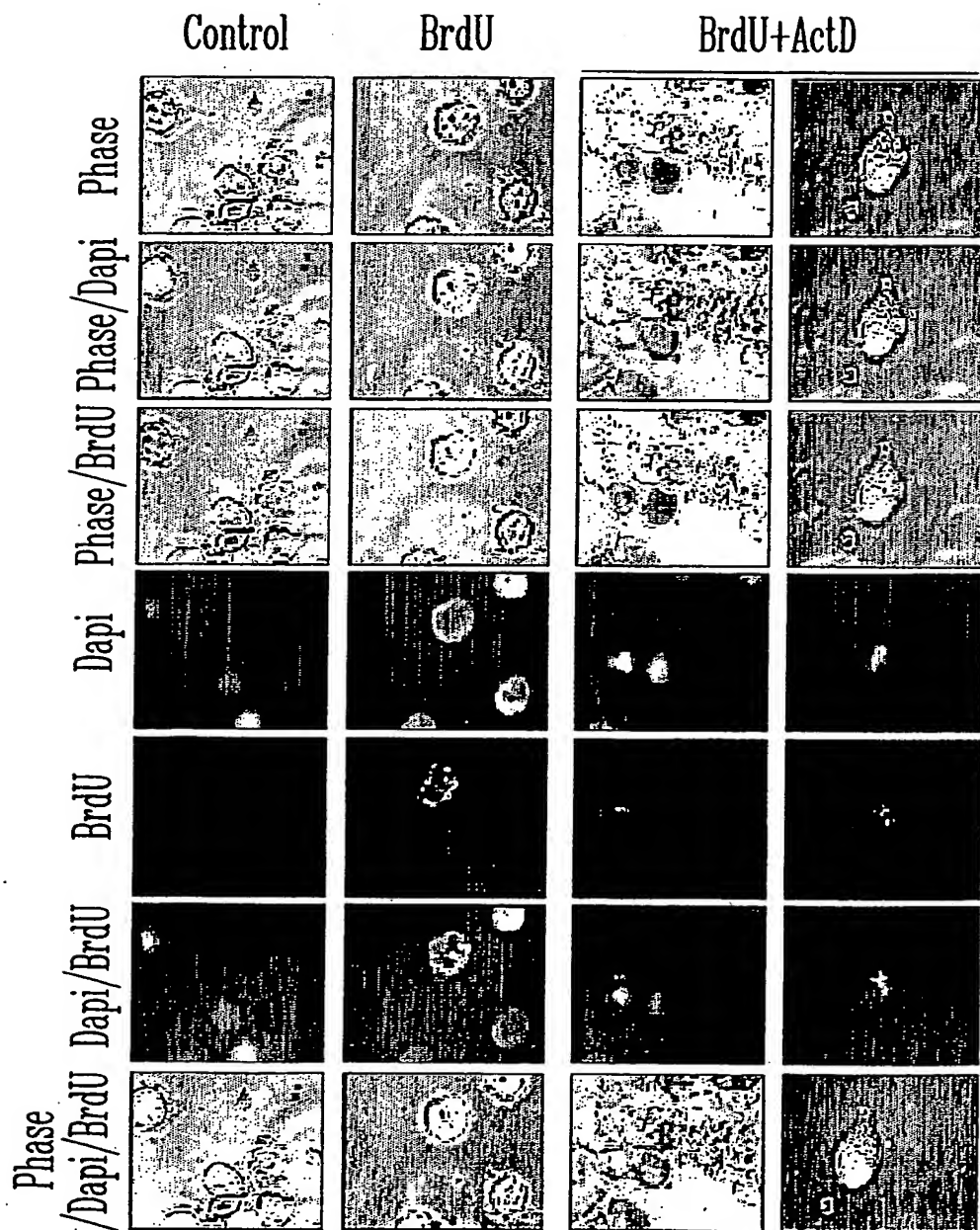


FIG. 23C



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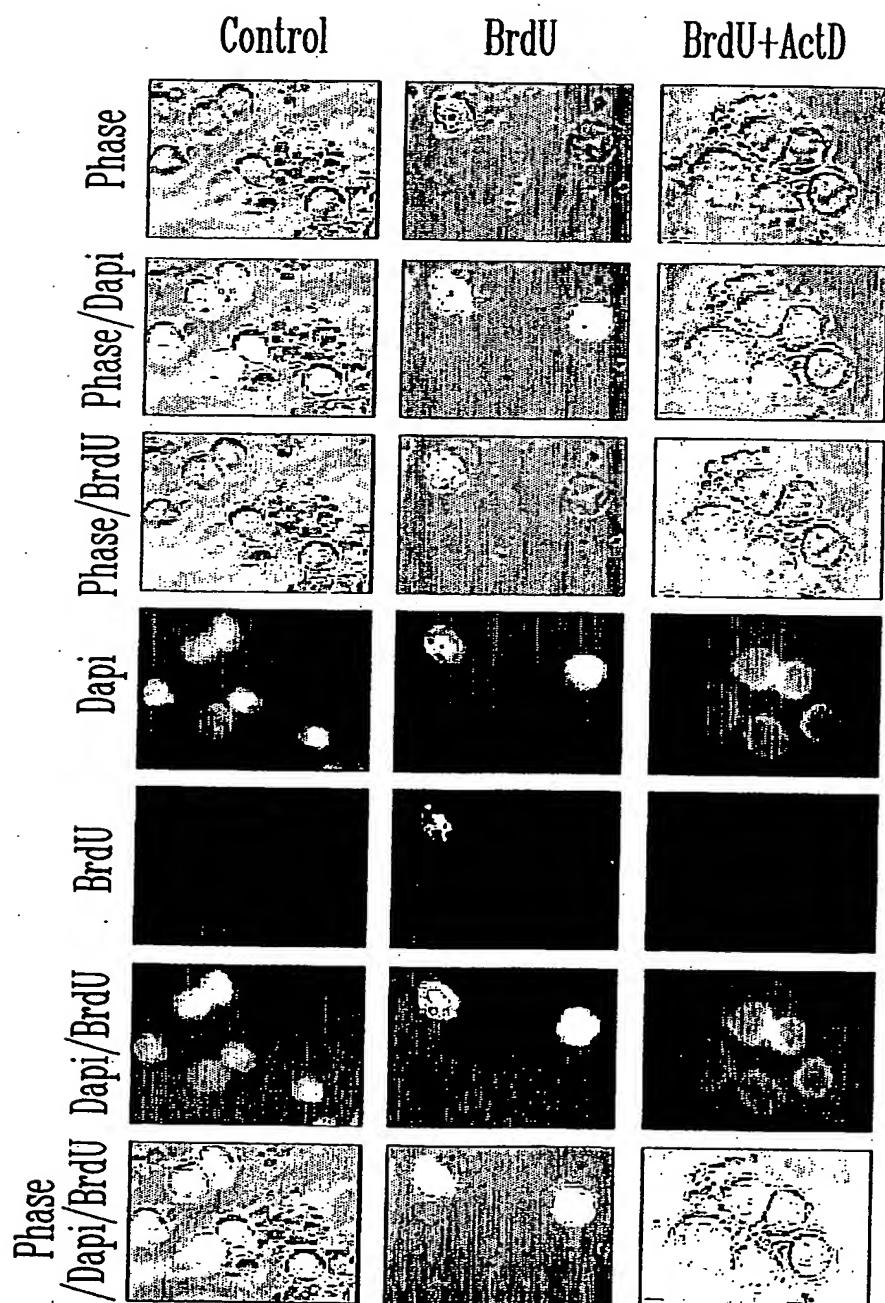
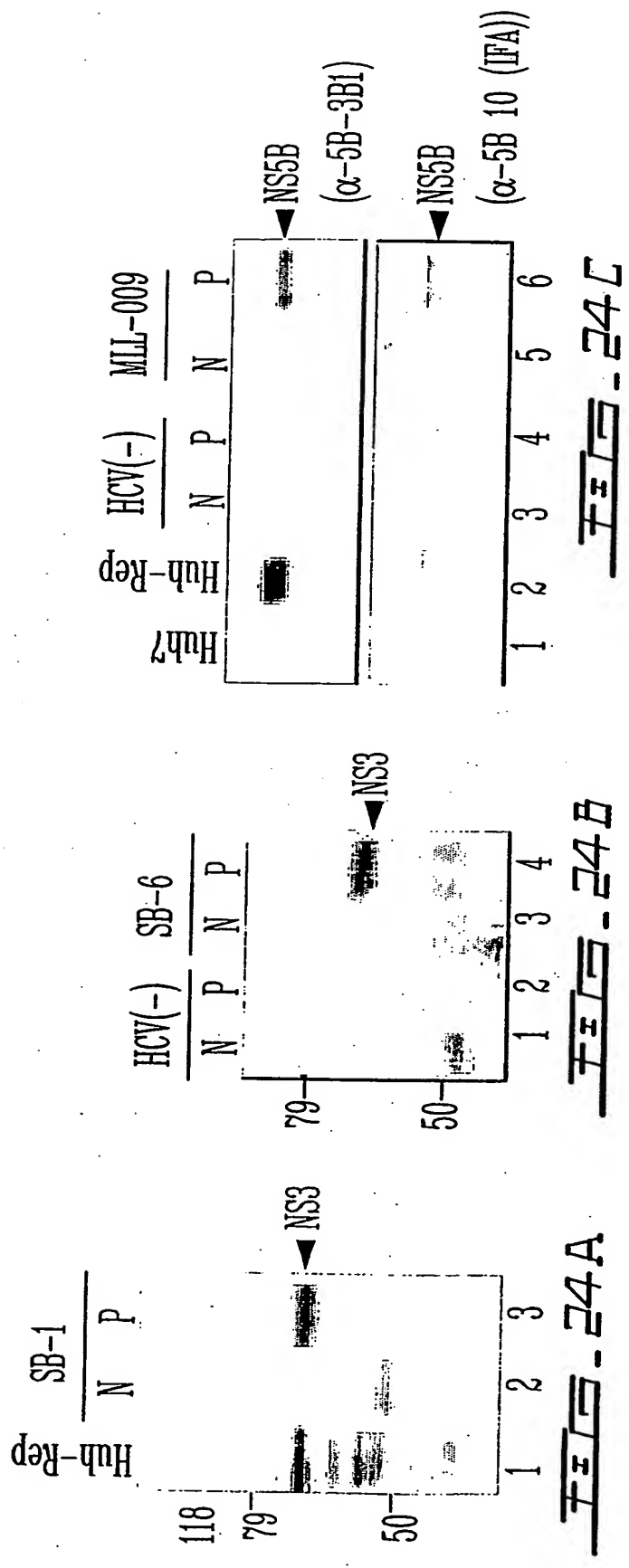


FIG-23D

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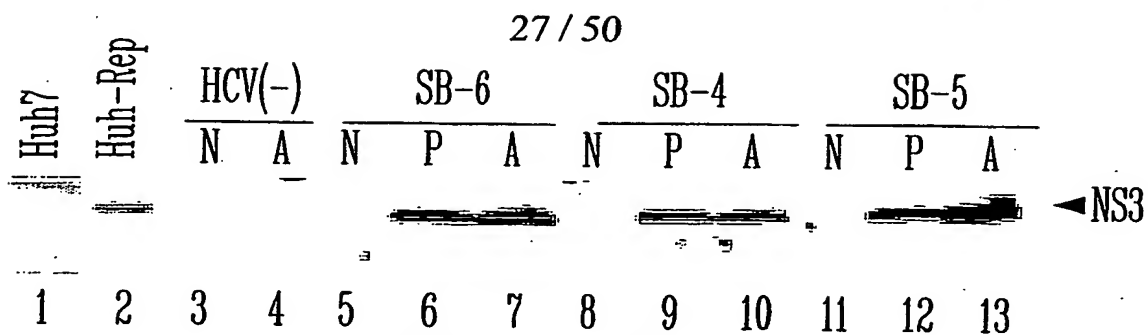


FIG. 24 D

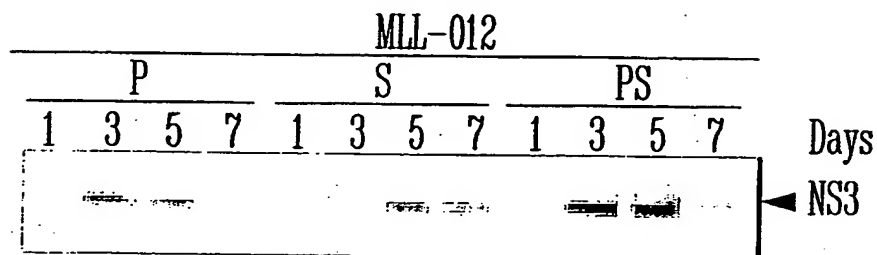


FIG. 24 E

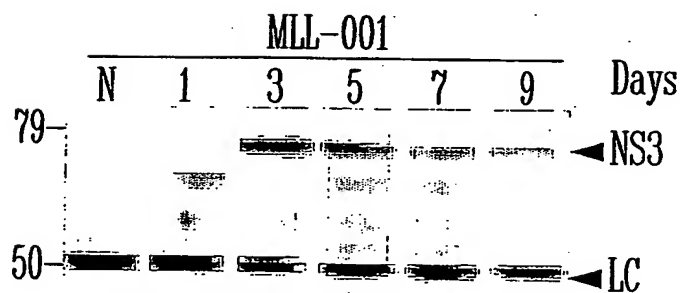


FIG. 24 F

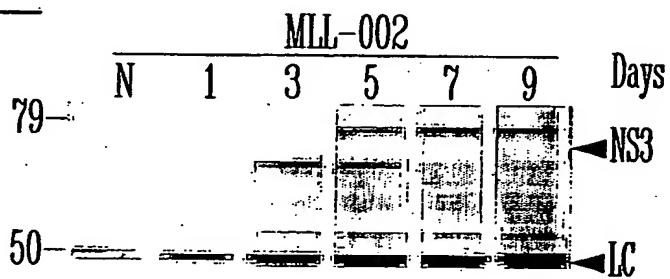


FIG. 24 G

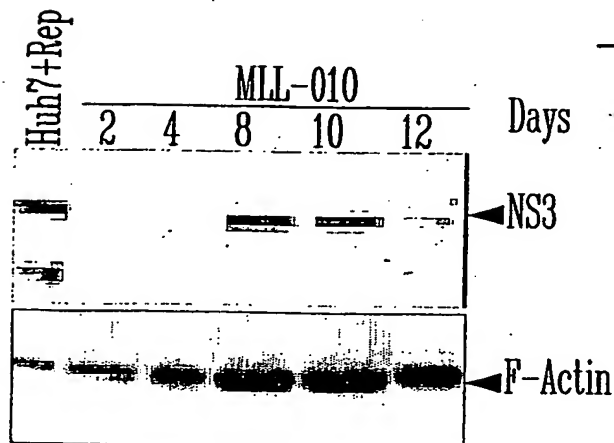


FIG. 24 H

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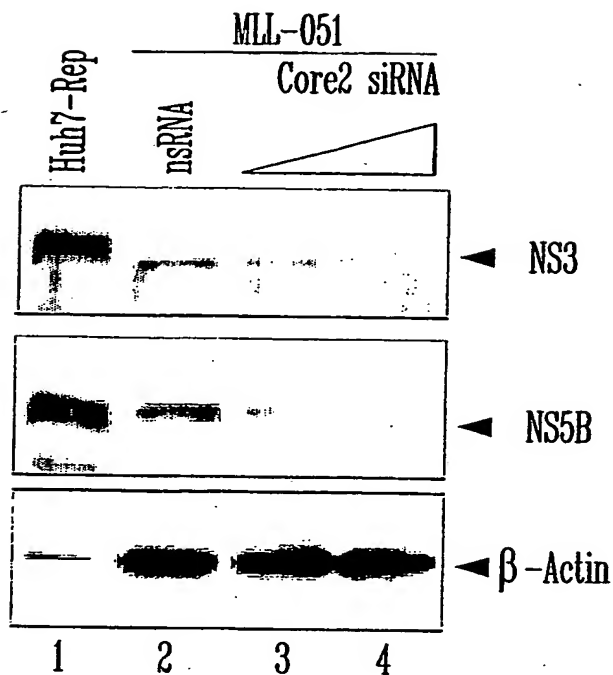


FIG. 24I

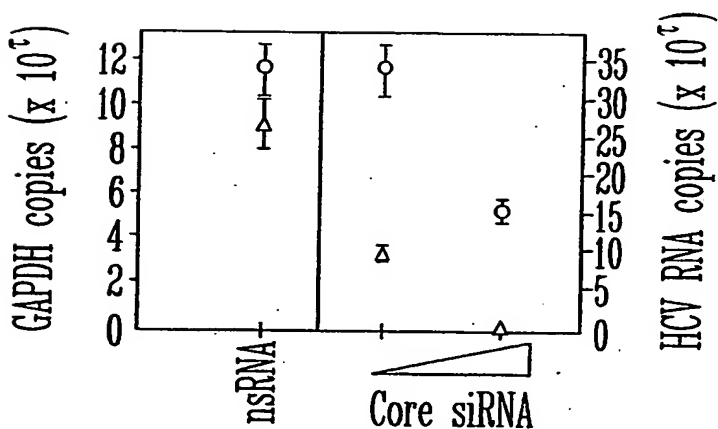


FIG. 24J

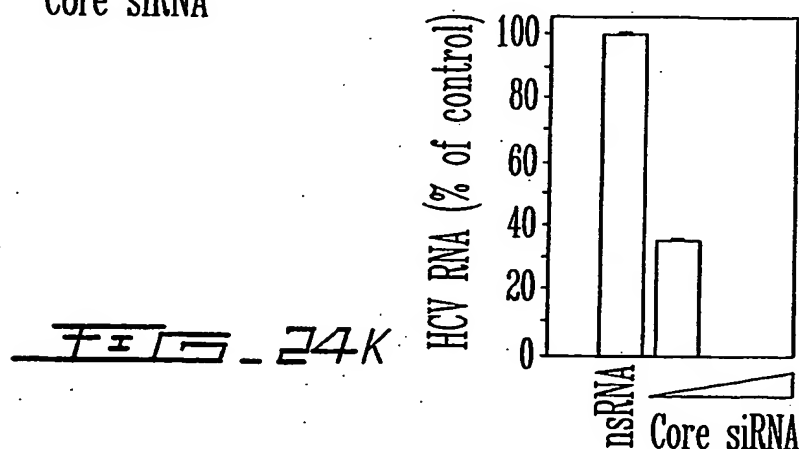


FIG. 24K

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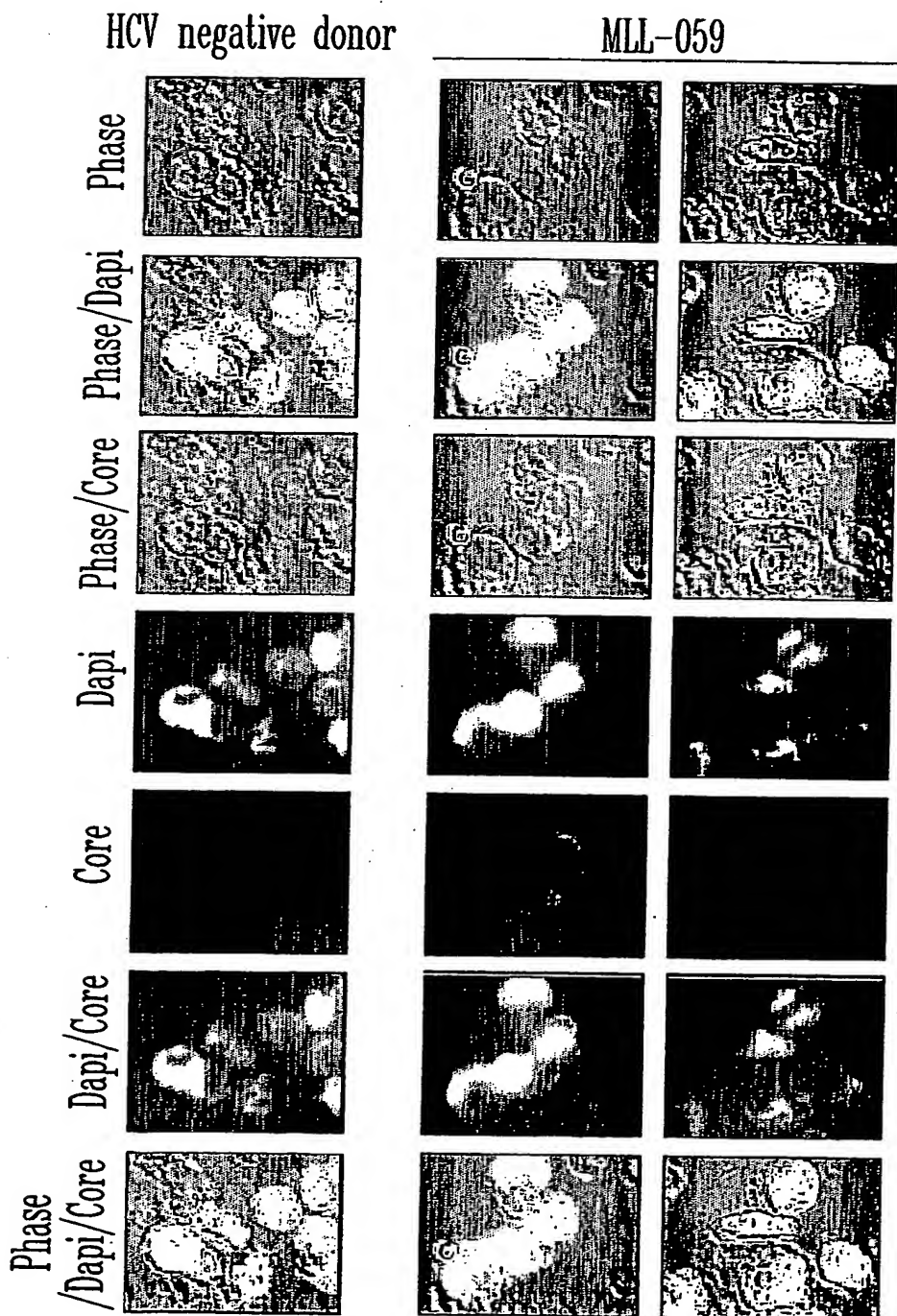


Fig. 25

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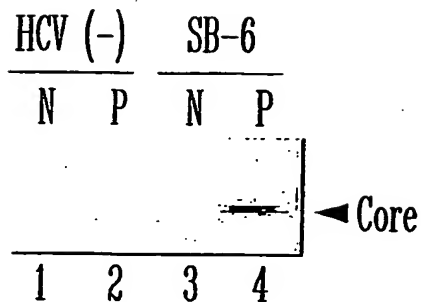


FIG. 26A

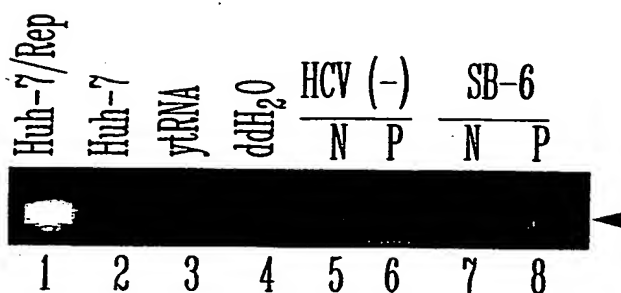
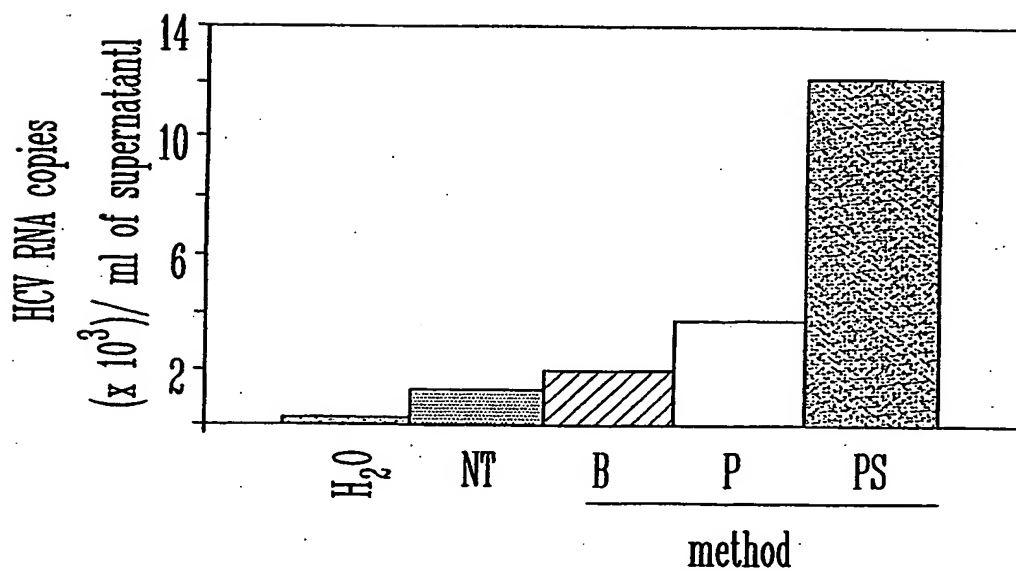


FIG. 26B



SB-5

FIG. 26C

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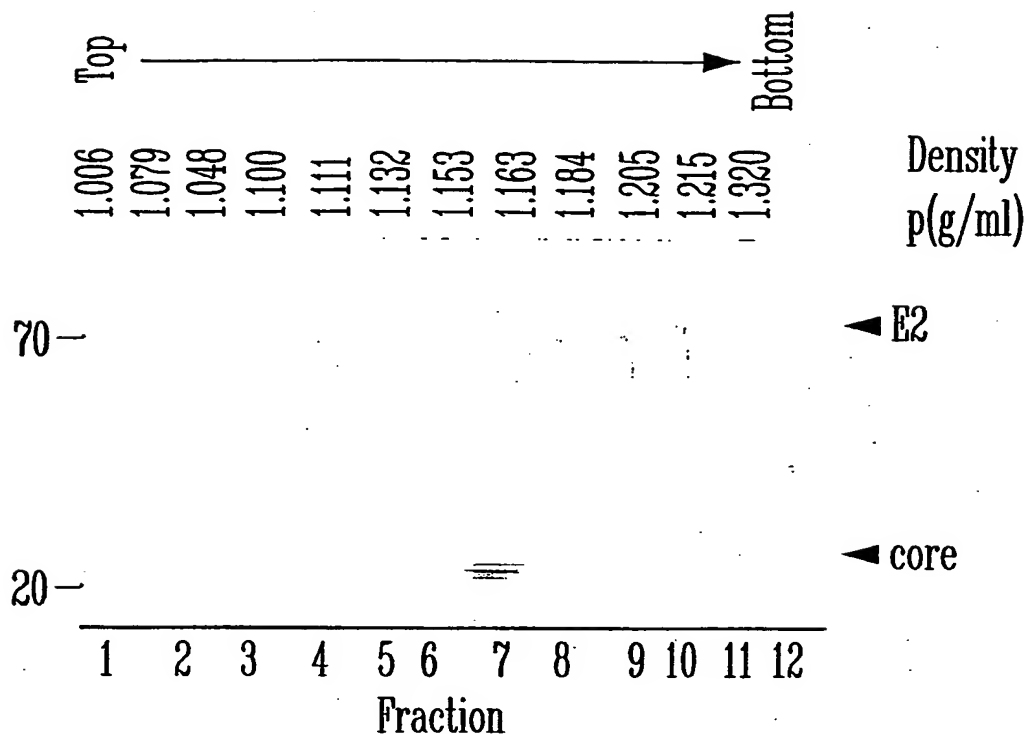


FIG. 26D

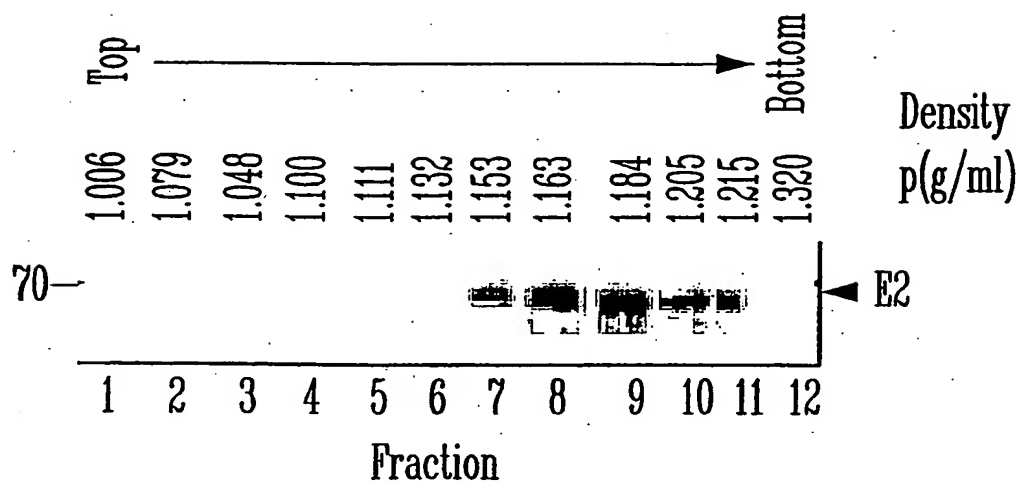
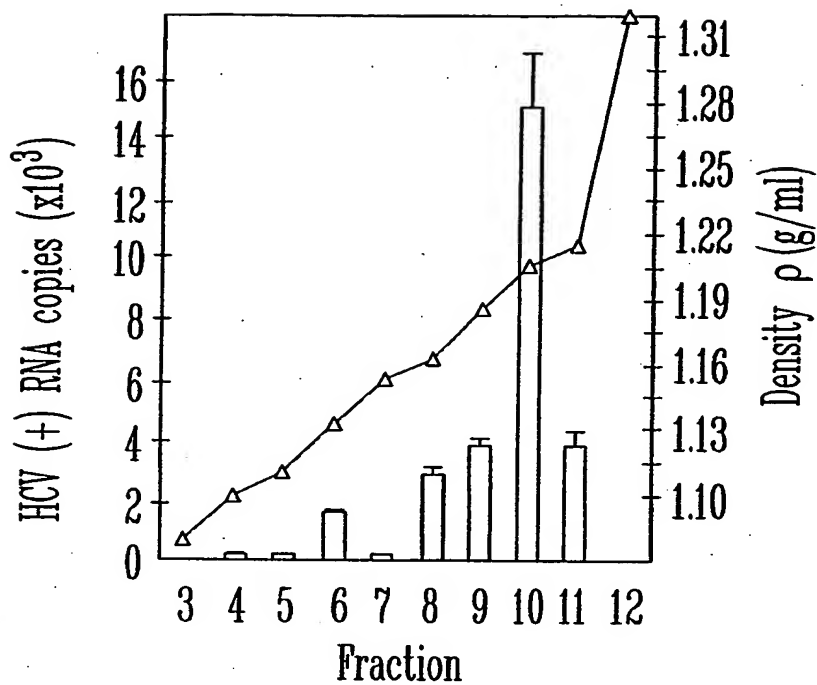
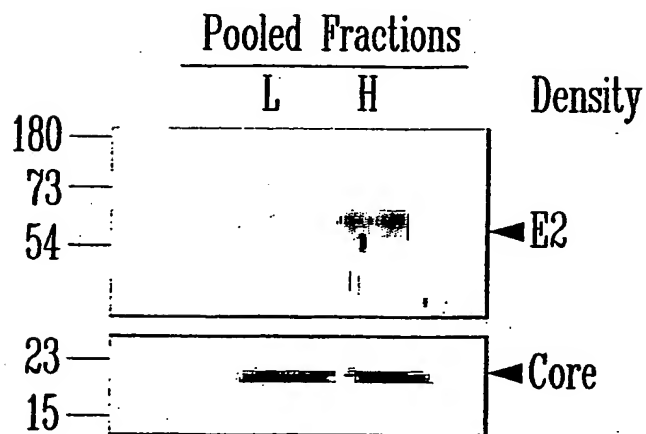


FIG. 26E

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FIG. 26FFIG. 26G



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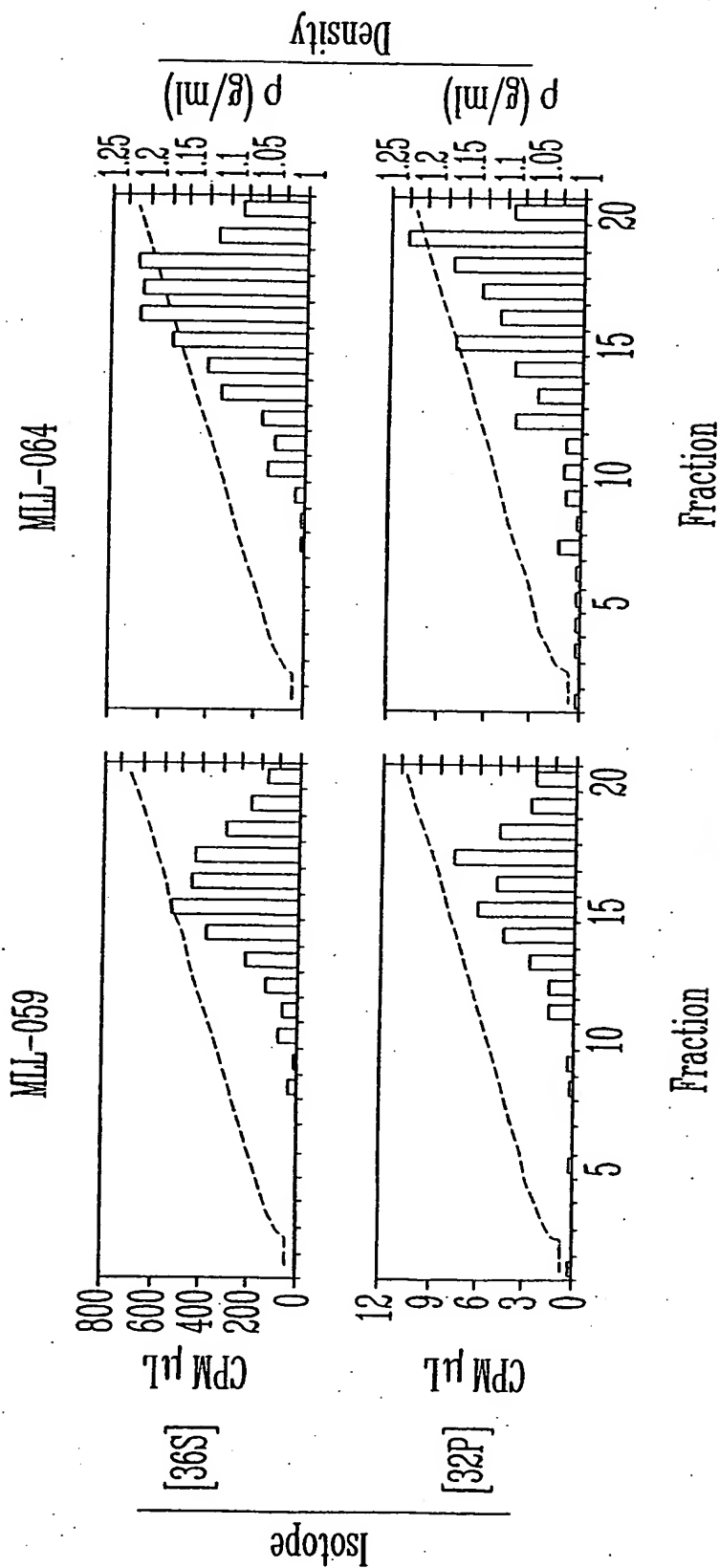
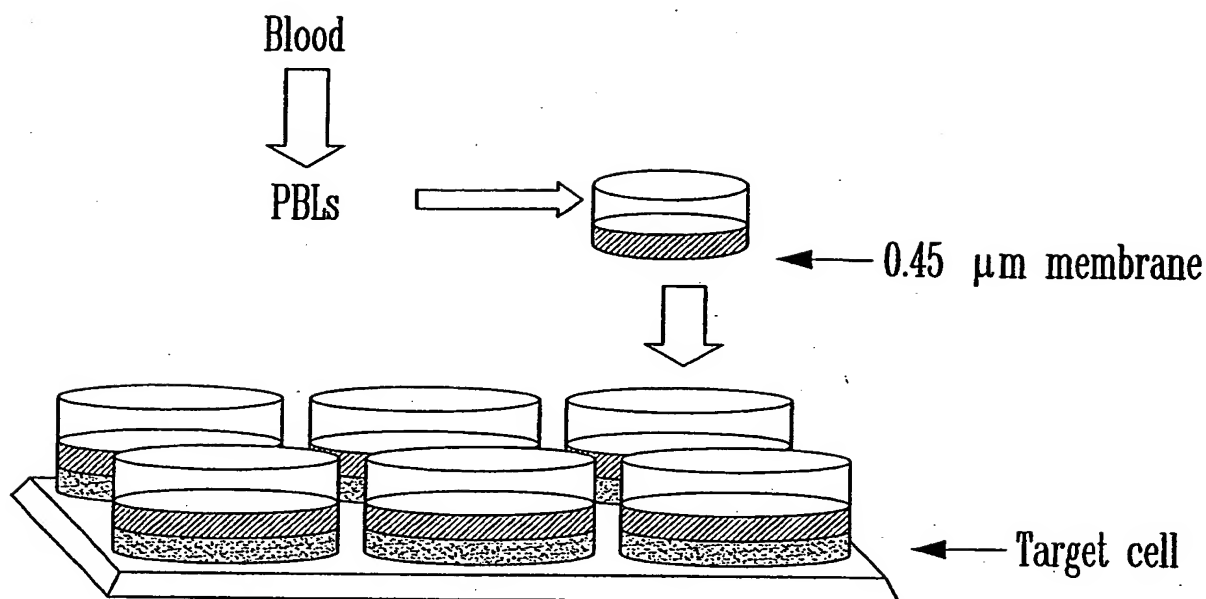
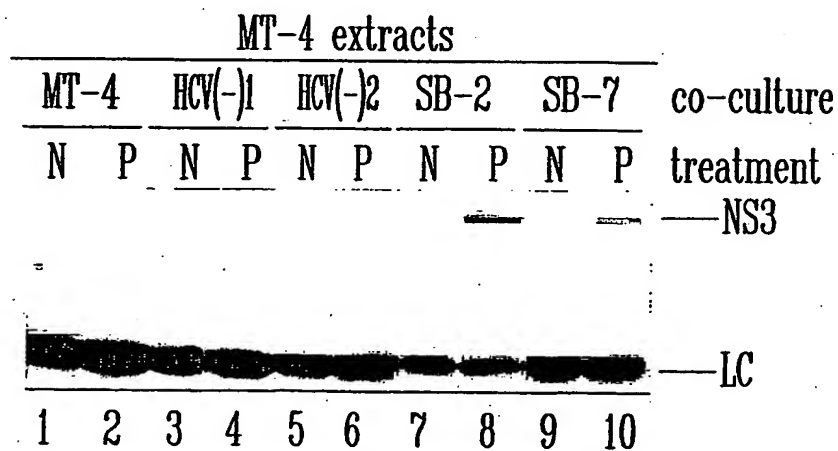


FIG. 26H

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FIG. 27AFIG. 27B

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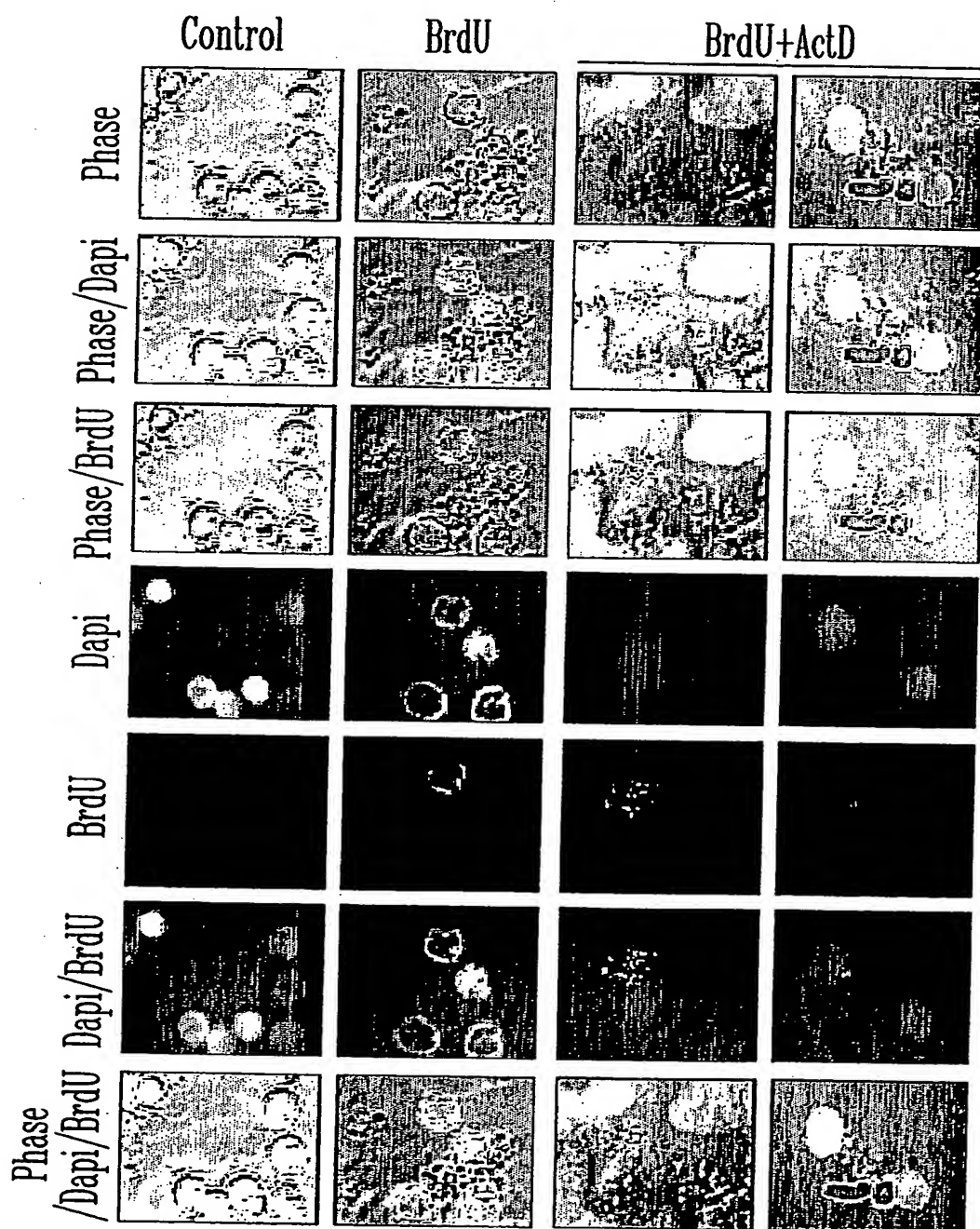
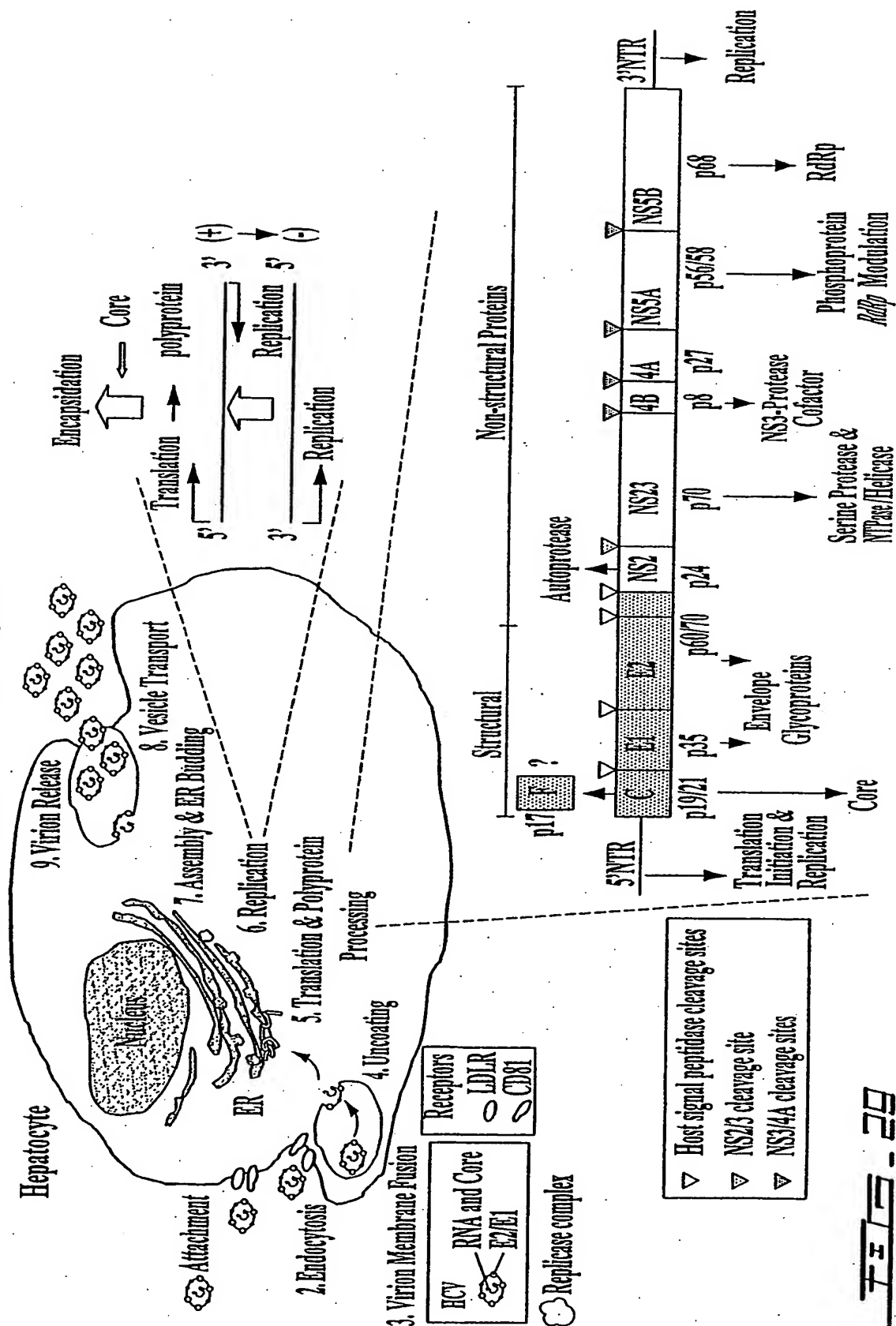


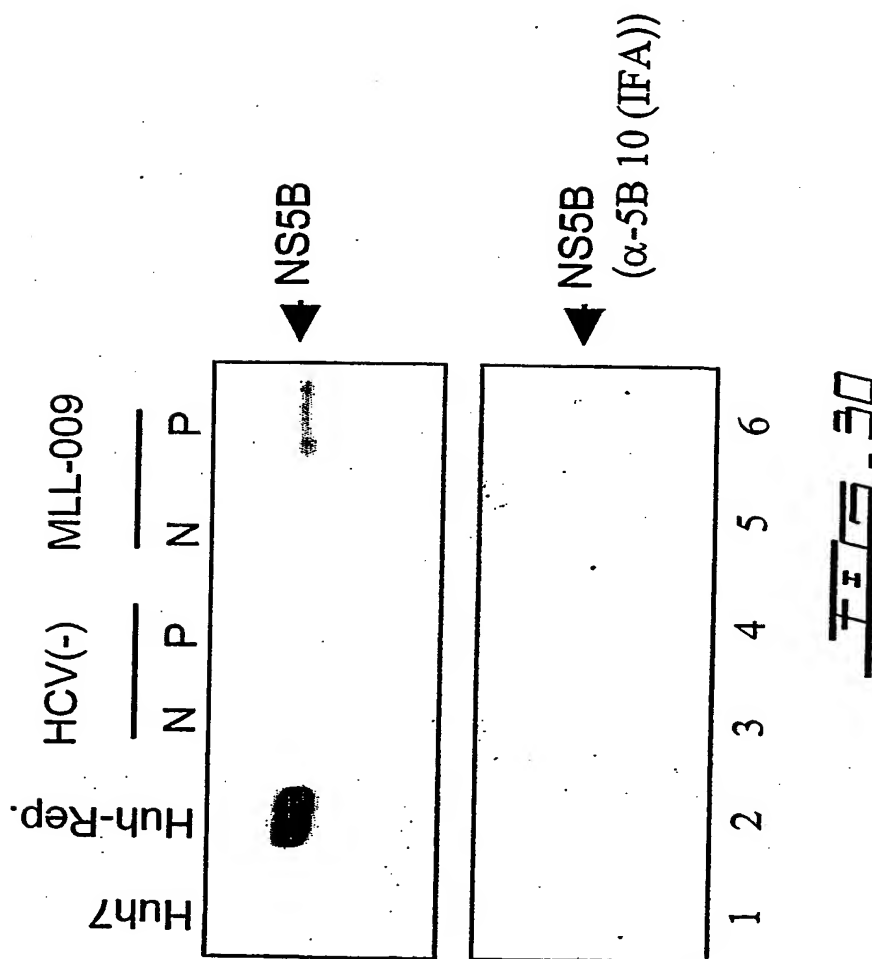
FIG. 2B

## HCV Replication Cycle



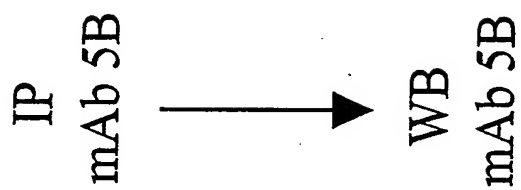
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MLL031 + MLL 032  
HCV(+)

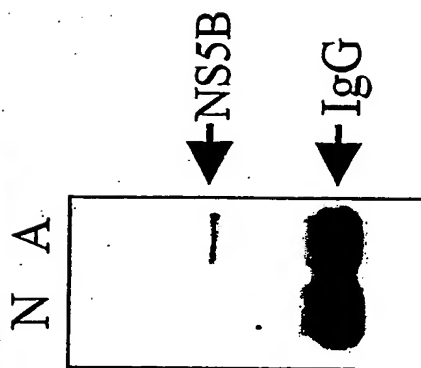
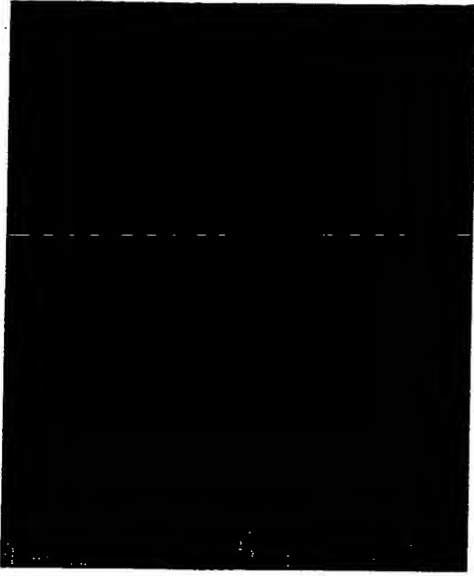


FIG. 31

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Anti-Core



Dapi



Phase/Dapi/Anti-Core



Dapi/Anti-Core



Phase



FIG. 32

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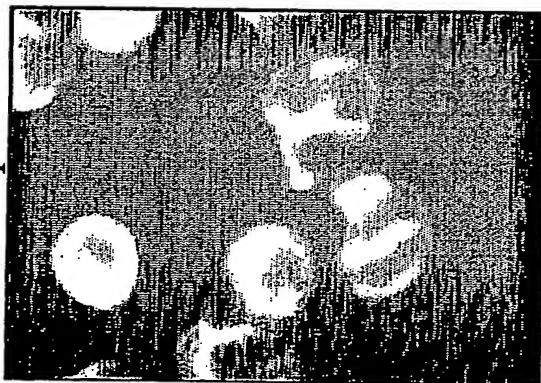
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FIG. 33

Anti-Core



Dapi



Phase



Phase/Dapi/Anti-Core



Dapi/Anti-Core

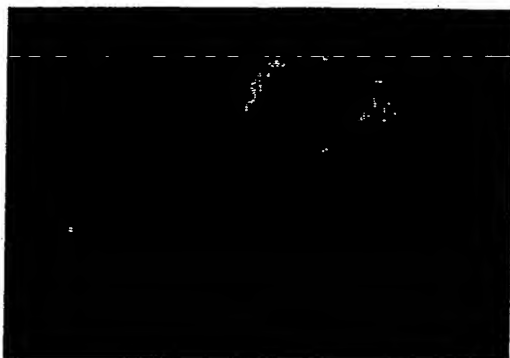




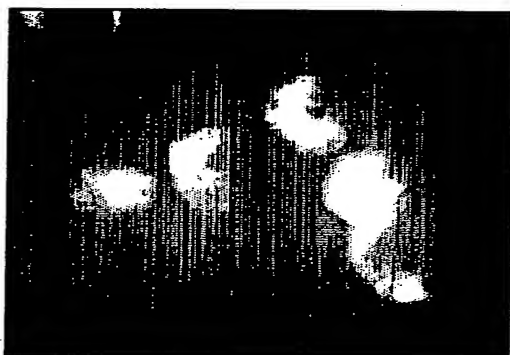
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Anti-Core



Dapi



Phase



Phase/Dapi/Anti-Core



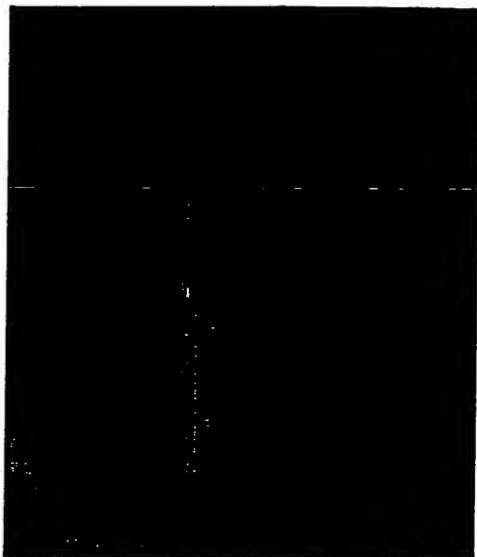
Dapi/Anti-Core



Fig. 34

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Anti-Core



Dapi



Phase



Phase/Dapi/Anti-Core



Dapi/Anti-Core

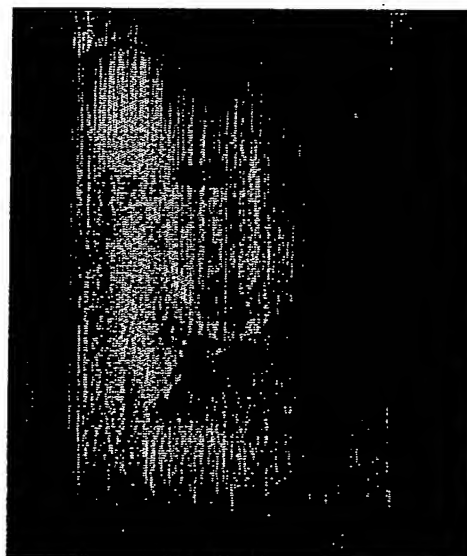


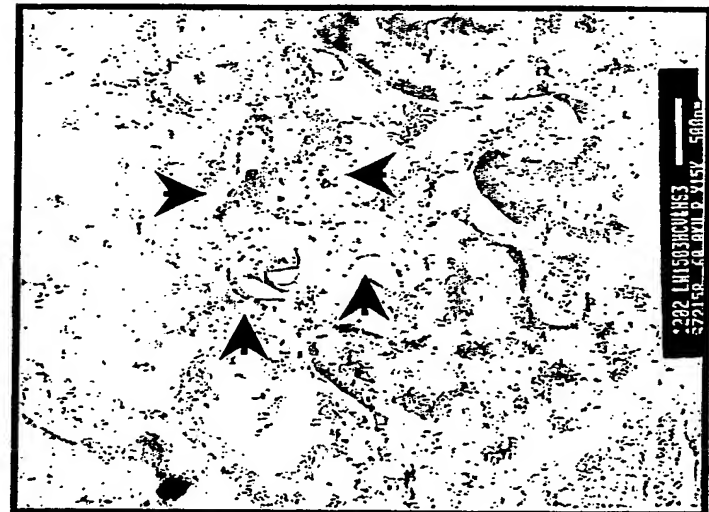
FIG. 35

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FEL-36C



FEL-36B



FEL-36A

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FIG. 37

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# Virus partial purification.

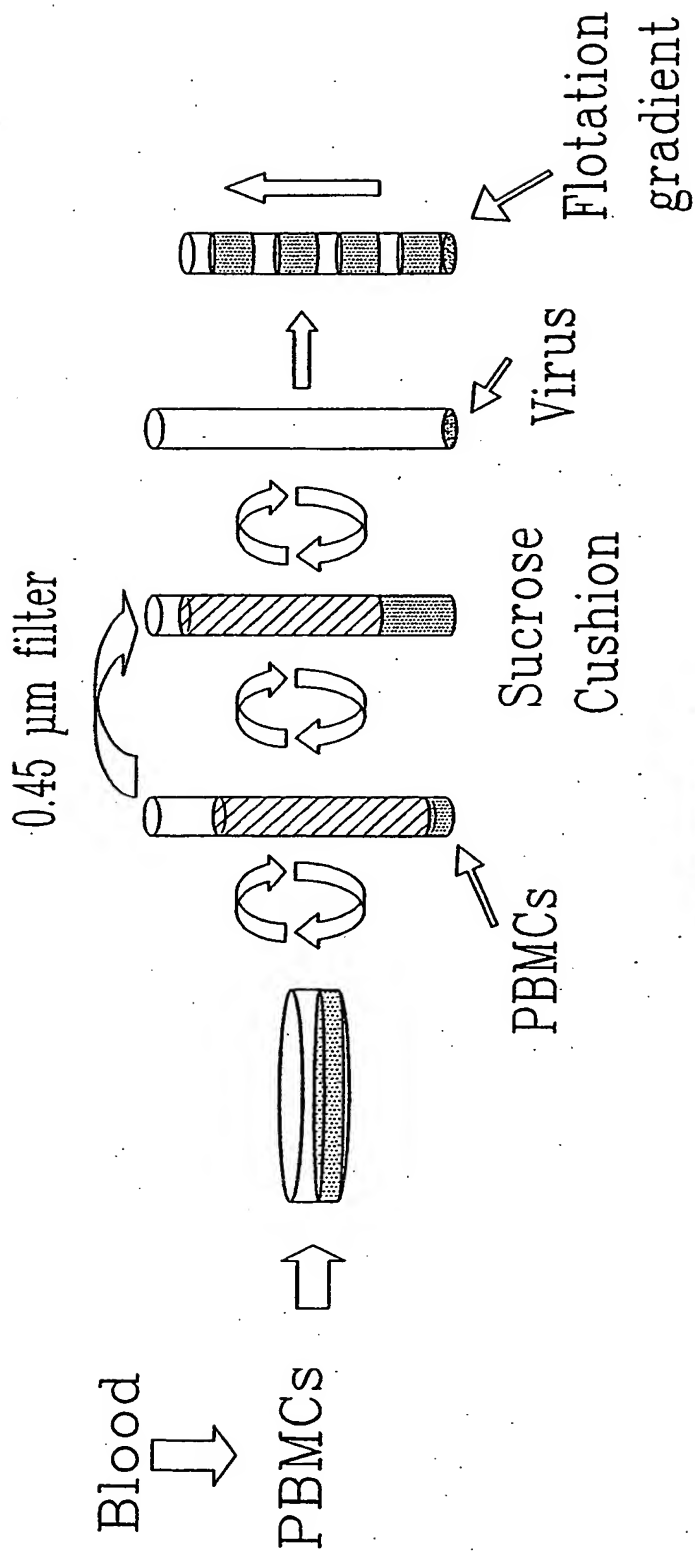


FIG. 3B

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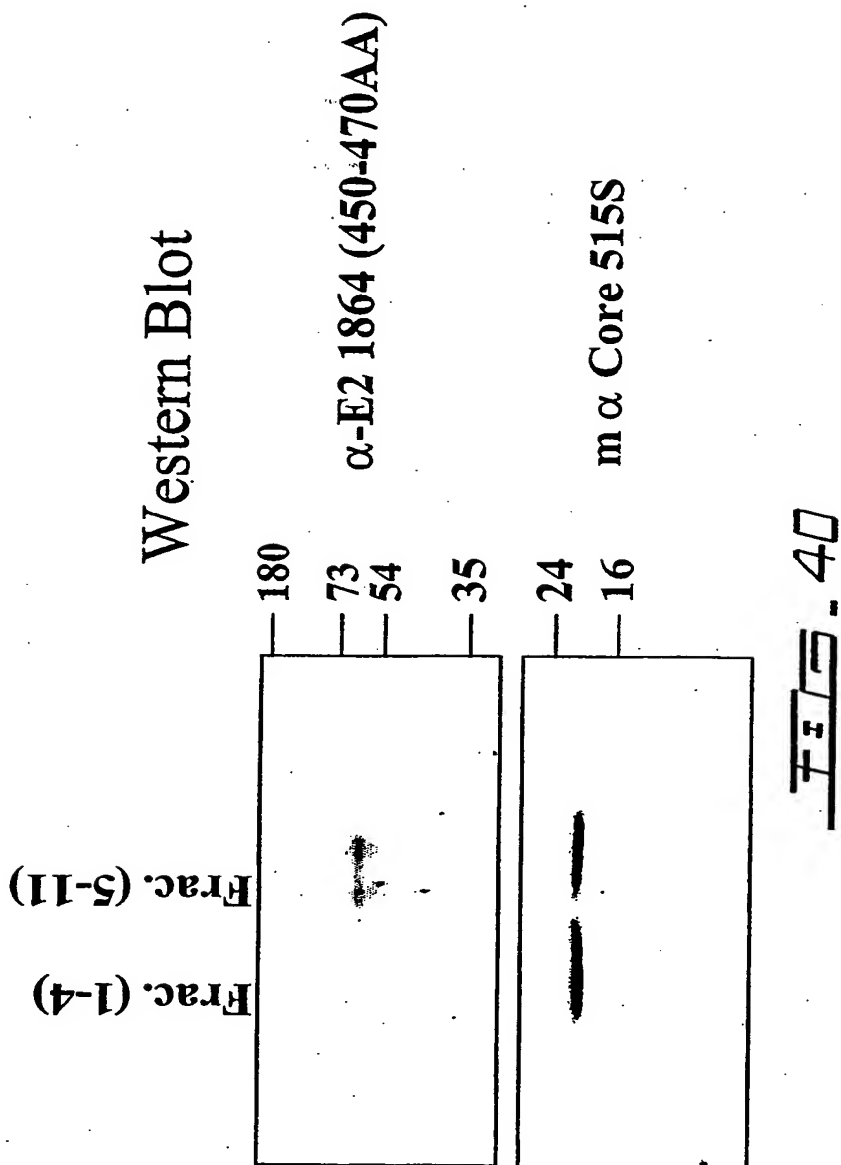
Density Range (g/ml)	Source	Reference
1.15-1.20	HCV-LP in VSV vector	J. Virol (2002) 76, 12325.
1.14-1.18	HCV-LP in insect cells	J. Virol (1998) 72, 3827.
1.12-1.17	Plasma chimps	J. Gen. Virol (1994) 75, 1755
1.09-1.21	Plasma chimps	J. Med. Virol (1991), 34, 206.
1.13-1.17	Plasma chimps	J. Virol (1993) 67, 1953
1.063-1.21	Serum infected donors	J Med Virol (2002) 68, 335

1.11-1.215	HCV(+) PBMCs	-----
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FIG. 39

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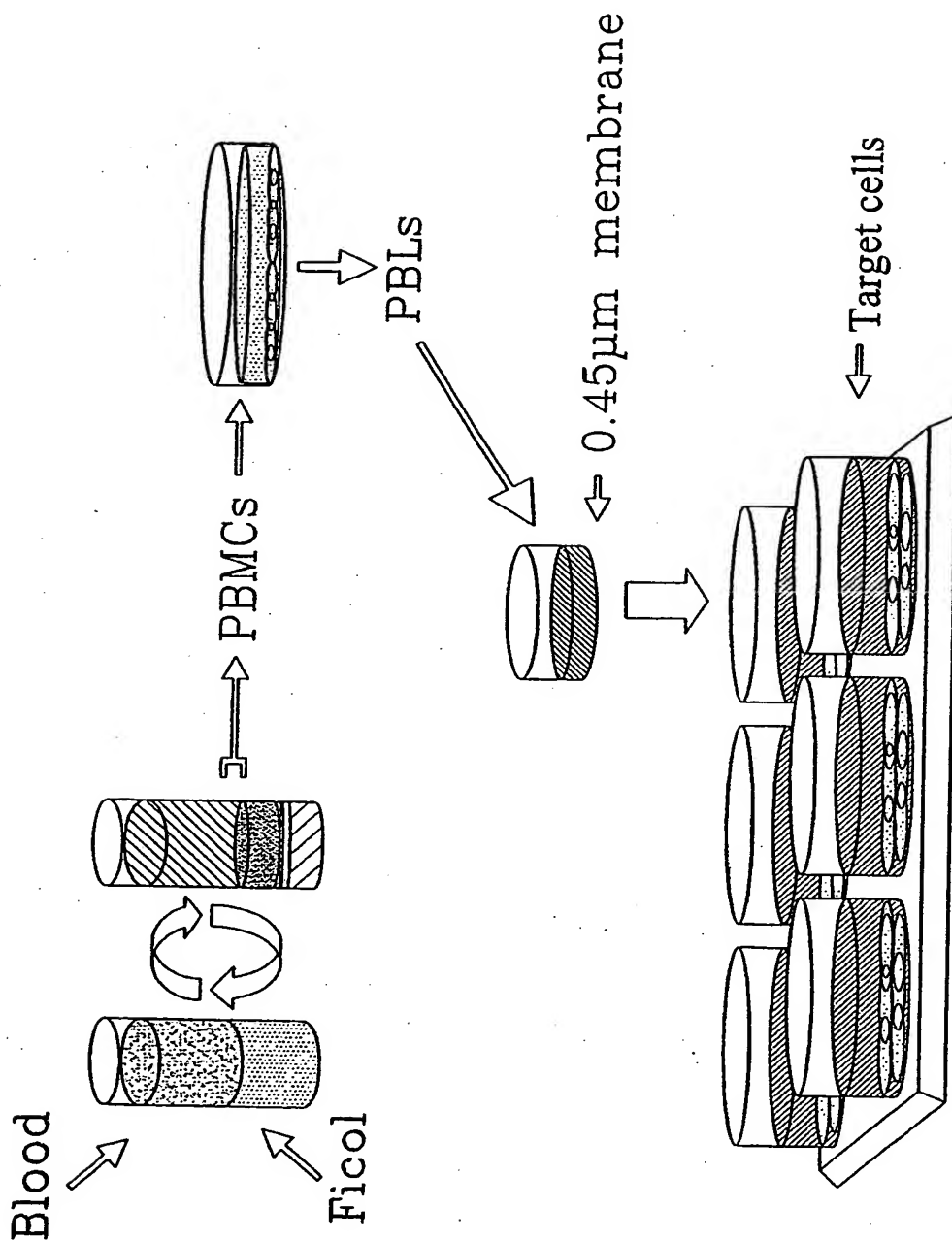


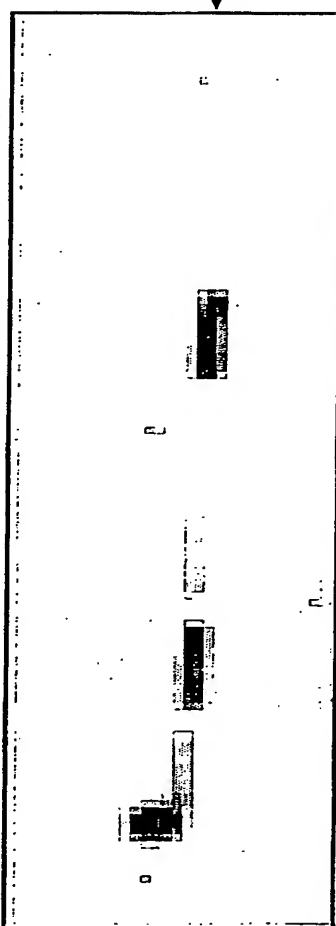
FIG. 41



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MLL-0015

<u>P+S</u>		<u>P+S/ <math>\alpha</math>-Inf</u>							
1	3	5	7	1	3	5	7		
								Days of treatment	
								NS3	

NS3

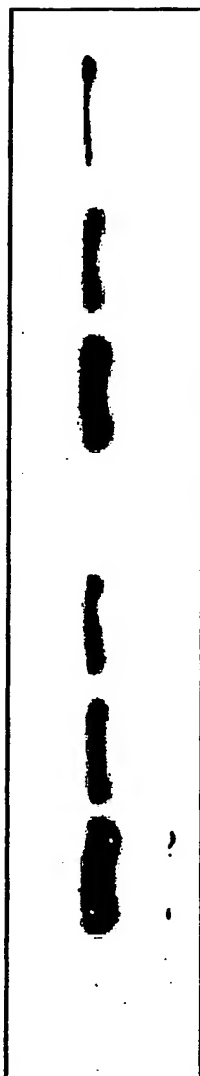
Fig. 42

# HCV 1a

PHA PHA/COMPOUND X

1 3 5 7 1 3 5 7

Days of treatment



← NS3

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COMPOUND X: 100 $\mu$ M  
in  $\alpha$ -NS3 1G3D2

FIG. 43

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